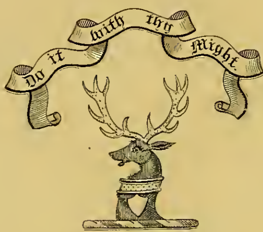

Bertram H. Buxton.

The Inflammation Idea in General Pathology

By

W. H. Ransom, M.D., F.R.S. F.R.C.P.
Consulting Physician to the General Hospital, Nottingham.

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[illegible] an appropriate one than I then thought. It has, in fact, still to be justified; for although the two processes have not been completely separated upon sufficient grounds, neither have they as yet been sufficiently shown to be so near to each other as to be now, and rightly, placed in the same category. Most pathologists who treat of inflam-

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CORRIGENDA

Page 33, line 5 from bottom, for "specificially" read "specifically."
" 38, " 25 " for "*Cecidomya*" read "*Cecidomyia.*"
" 38, " 23 " for "*Hormomya*" read "*Hormomyia.*"
" 58, " 30 " for "*Aphillothrix*" read "*Aphilothrix.*"
" 58, " 29 " for "*Hormomya*" read "*Hormomyia.*"
" 60, " 30 " for "*Aphillothrix*" read "*Aphilothrix.*"
" 60, " 26 " for "*folii*" read "*scutellaris.*"
" 311, " 31 " for "*Atyoida*" read "*Atyoïda.*"
" 311, " 17 " for "*membranaceus*" read "*membranaceous.*"

The Inflammation Idea in General Pathology

Part I

SECTION I

THE QUESTIONS ASKED, STATED IN THREE GROUPS OF ACCEPTED FACTS, AND THE INFLAMMATION IDEA IN GENERAL PATHOLOGY

§ 1. In 1892 I gave an address in the Section of Medicine at the Nottingham Meeting of the British Medical Association, "On Some Diseases of Plants compared with those of Man." The conclusions then reached, in so far as they relate to the plant-diseases treated of, are still tenable in the main, although they demand some, perhaps minor, corrections. However, the comparison I then drew between the growth of galls in plants and inflammation in man was then, and is now, less generally accepted as an appropriate one than I then thought. It has, in fact, still to be justified; for although the two processes have not been completely separated upon sufficient grounds, neither have they as yet been sufficiently shown to be so near to each other as to be now, and rightly, placed in the same category. Most pathologists who treat of inflam-

mation in the higher animals ignore the question of any disease-processes in plants strictly analogous to inflammation in man, and some explicitly deny their possibility.

I will therefore now endeavour to give a candid reconsideration to the position then avowed, and summarised in the following passages :—(p. 1) "Inflammation in Plants might have been the title of this address, as it will deal almost solely with that process, which, as I define it provisionally, may be considered as the reaction of living cells to irritation"; and again (p. 19), "That the reactions of all living tissues to irritants are rightly considered as inflammations, I think will receive general assent. Nor can I doubt your support of the proposition that a general theory of inflammation should include all organisms." That these assumptions were much too sanguine, I now grant, and do suitable penance for them. Again, I ventured then to suggest as a sufficiently comprehensive definition of inflammation the following :—"In virtue of those necessary and inherent faculties by which all organisms repair injuries, living cells react in response to true irritations by a proliferation with modifications directed by the irritant, and not beneficial to the organisms in which the process occurs."

I purpose here, so far as is possible without bias, to inquire anew what relations, if any, exist between typical inflammations, as almost universally accepted in the higher animals, and the disease-processes in plants above referred to; how far they are really analogous or comparable; and whether or no they are properly to be designated by the same term; or if not, whether or no they may be included in one larger common pathological group.

In so doing, I shall reverse the point of view and, instead of approaching the problem from the standpoint of the phyto-pathologist, shall do so from the position of

the student of human pathology, which has the advantage of having been longest studied, of having given us the terminology in use, the dominant ideas in regard to the series of phenomena presented and the most elaborate and detailed observations thereon. The object being thus viewed from its two chief aspects, may reasonably be expected to appear more proportionate, and even distinct, than when seen from either alone; and I hope a more consistent and intelligible idea may then be formed of what it is we should mean by the term inflammation in general pathology, considered as a branch of general biology, than up to the present has been the case. Each aspect of the problem has its own special advantages, as well as disadvantages; but both being duly studied, the whole may be, I think, better understood, as each may supplement or correct the other; and the proportionate value of each chief factor may appear more clearly.

§ 2. Viewing, then, both kingdoms of nature in broad outline together, the questions before us may be briefly stated thus, in three groups of accepted facts:—

A. It is an observed fact, widely, I think universally, accepted, that all living organisms are liable to many casual non-fatal injuries, and that a series of changes follows them, by which such injuries are healed. This is spoken of as *Repair* of injury, and has been well called a "universal physiological law of nature" (Burdon-Sanderson).

B. It is also a generally accepted fact, that, certainly in some, perhaps in all, living organisms, after some apparently similar injuries, a different series of changes follows, during or by which the process of healing is arrested or perverted and damage is done. This is spoken of as *Inflammation* when met with in man and

in some other organisms; and when a similar series of changes is met with, but is not preceded or accompanied by any discoverable injury, the same term is used to indicate it. It is one of the aims of this essay to ascertain in what organisms this process or its equivalents are met with, and to this end it is necessary to learn how it can be recognised, wherever it is met with, and, when it is not seen in its typical form, what are its equivalents.

C. It is also similarly accepted as a fact, that, in a large proportion of the cases in which the process of *Repair* has been so arrested or perverted by the series of changes called *Inflammation*, in some organisms whether preceded by an injury or not, this process ceases after a time; and then repair dominates, and healing is the result. This is spoken of as *Recovery*: and the expression is used here in this sense, and so with a technical limitation to this frequent consequence of *Inflammation*.

§ 3. From this summary statement of generally accepted facts I conclude, though as yet only provisionally, as follows:—That the faculty of *Repair* of casual injuries is to be regarded as an evolved, necessary, normal and beneficent faculty of all organisms, without which they could not maintain themselves in life: that *Inflammation*, when it is met with, is not an evolved, necessary, normal faculty; but is a casually intervening, abnormal and damaging process, and, so long as it lasts, antagonizing repair; it is not, however, as yet generally accepted as occurring in all organisms: that in those organisms in which *Inflammation* is known to occur, when it ceases, *Recovery* often takes place in virtue of the persistence in the focus throughout the abnormal process, of the evolved, intrinsic, normal, reparative faculties, which had been misdirected but not destroyed by the irritant

actions; and although often the final result may not restore the exact condition which had preceded the injurious irritation and the *Inflammation*, yet does it always result in a beneficent approach thereto, and it is in effect a repair, even if only by compromise. These conclusions are not in accord with the current, dominant teachings, although they rest upon the facts stated above as accepted. Provisionally, they seem justified thereby; and they include both plants and animals.

§ 4. As the title of this essay includes the inflammation idea, and also that of general pathology, it is required to form as clear a conception as is possible of both. Enough has been said by way of introduction to the former, but something further is requisite in respect of the latter, seeing that the expression general pathology is not generally used in the wider sense I here adopt. I will take as a fair illustration of this broad statement, E. Ziegler's *Handbook of General Pathology; or, The study of the causes, the nature, and the course of diseased vital processes* (vol. i., tenth edition, 1901). He says, in the introduction to this volume: "General pathology, the study of diseased life, includes the task of a research into all the diseased vital processes in all directions, that is, not only their essentials and significance or meanings, but also their causes and origins, as well as ultimately their courses and results."

He rests pathology, as physiology, upon the results of studies chiefly made in man and his allies, and makes general pathology the equivalent of pathological physiology so derived. He, however, does not include in his researches, as they are here given, "all directions," but limits them largely, almost exclusively, to the "diseased vital processes" as met with in man; and to this extent he is not consequent. As a result, the manifestations of

the various "diseased vital processes" which he dwells on are not those which are met with in all organisms; but they are dominated by the characteristic phenomena of those changes with which we are so familiar in man. They are not to any adequate extent founded on extended comparative researches into the equivalent phenomena met with in other organisms; and the invertebrata, as well as plants, are practically ignored.

A tacit assumption apparently runs through the book, that, notwithstanding his expression "pathological physiology," we must seek the typical "diseased vital processes" studied in general pathology, not as we have sought the typical physiological ones, comparatively in all organisms in general biology, but in a certain subordination to the almost traditional pathology of man. In this position he is again somewhat inconsequent. True, he refers briefly to unicellulars, and to their possession of faculties of movement, of formative changes, as in cell-division, and of nutritive exchanges; and he shows some of the contrasts between them and the more complex multicellulars, especially mammalia and man, in regard to their more specifically endowed structures and functions: but he does not here take note of the fact that the cells of the multicellular organisms are elementary organisms, and that in them also, often even in their more complex and specifically endowed parts, they functionate much as do unicellulars in their essential and fundamental faculties of nutrition, growth, movement, and multiplication by proliferation or division.

Thus, although he calls Virchow "Meister," and dedicates to him this edition, he fails to adopt his views in regard to the cell, and its significance in pathology, and is again in this respect inconsequent.

His mental attitude in this regard is displayed in his

grouping of the questions, or the phenomena to be discussed in general pathology, as well as in the area of the field which he surveys. He does not subdivide the phenomena to be studied in "all directions" into those which are common to all living things and those met with only in some, nor indeed give any appreciable attention to the former; but mostly, almost solely, makes a study of the latter only.

A glance at his table of contents, and at the sections into which he divides his *General Pathology*, shows that, after a general survey of the causes of diseases and of the modes by which they are spread, chiefly within an organism, he deals with the defensive faculties, such as repair and immunity, in man; then with the circulatory and the lymphatic disorders; then with the regressive phenomena of degeneration and infiltration; then with hypertrophy and regeneration, transplantation and metaplasia of tissues; then with inflammation, acute and chronic, including herein its factors, as a complex process, containing regressive, proliferative, and vascular changes; then with new growths thought of as autonomous productions, of which the etiology is not given or known, but (he insists) as not infective or of parasitic origin; then with the malformations thought of as disorders of development, in the main of unknown etiology; and then with a somewhat irregularly placed special consideration of some parasitic agents or causes of diseased phenomena, as bacteria, blastomycetes and various animal parasitic organisms. The whole volume of general pathology thus rests upon divisions of the questions to be studied, which are traditional in human pathology, and not upon those which are or have been raised in regard to man in common with all other organisms.

§ 5. But the question I seek to answer in this essay is

not the inflammation idea only; it is also the general pathology idea; and without an understanding of the latter, in respect of its area of extension, I cannot very well deal with the former in its connection with general pathology. There can be no question that all organisms are liable to casual injuries of various kinds and degrees, and suffer from various "diseased vital processes" which, as they demand a study in "all directions," must all be included in any general pathology, properly so called. And, as the tacit assumption which Ziegler makes that the pathological phenomena we know most of in man afford valid types of all such "diseased vital processes" in all other organisms, is not legitimate; and, as also his assumption that their equivalents in the vast groups of lower animals and plants can be excluded from view without loss of a true conception of the whole series of events, is equally illegitimate,—I am justified in disputing both assumptions, and in asking for evidences derived from all organisms as foundations of a general pathology.

It is possible, even probable, that in the whole series of events there may be some of the "diseased vital processes" which are limited only to some organisms, or parts of them, or are limited by certain conditions; but this, if so, demands proofs, and it may not be assumed to be in particular cases without evidence, and still less can it be used as a type. This exclusive position, without proof, even without inquiry, so far as this book is concerned, is just what Ziegler has taken in regard to inflammation—a pathological process, or series of abnormal phenomena, which is universally allowed to be one of the most important in a general pathology. He restricts his conception of it to a group of events which can only appear in some parts of some living organisms; he separates it much from repair and regeneration, without

showing intelligibly their real connections of interdependence, from degenerations or regressive changes, from many progressive events, and from new growths and malformations in an equal degree, and with as little adequate attention to their real and mutual relations in the affected organism.

In this way general pathology, as he teaches it, is a narrow and very limited study as to its area; and inflammation is a much restricted idea, not met with in all organisms, and not manifested even in the whole of those in the area which he includes in a general pathology, as he uses the expression.

§ 6. To each of these positions I raise objections, and in the course of this essay shall seek to justify them, show that general pathology deals necessarily with all living organisms, and that inflammation has very wide relations to them all. I have dealt with E. Ziegler as an example only of most systematic writers on general pathology; and, without here dealing with others similarly, may add that, except Virchow and Paget, I remember none who do not in the main take up a somewhat similar position.

It will be convenient, is perhaps even necessary, here to pursue the natural order in which the phenomena to be investigated are met with, and to study together, and separately, each of the three accepted groups of facts, in plants and in animals, with the view of showing, as clearly as possible, their differences and their resemblances, and ultimately their co-ordinations, if any there be. I am not without hope that this comparative method may throw light in some dark places.

SECTION II

THE QUESTIONS ASKED, STUDIED IN THEIR ESSENTIAL SUBDIVISIONS, SO AS TO SHOW THE MUTUAL RELATIONS OF THE FACTORS INVOLVED IN THE THREE GROUPS OF ACCEPTED FACTS, AND THEIR MANIFESTATIONS, IN PLANTS

§ 7. If we consider first and separately plants, it can be said that the study of *Repair* of massive and cryptic injuries, and of the growth of galls, including therewith all cecidia, presents us with the phenomena to be investigated, relatively more easy to observe and to deal with experimentally, than does the study of *Repair* of a simple traumatic injury and of typical *Inflammation*, or of *Recovery* after it, in man and in the higher animals. Phytopathologists have availed themselves of the opportunities so afforded with such a large measure of success as to justify a hope that students of animal pathology may derive assistance by connecting the two studies more closely than has generally been done hitherto. *Recovery* after inflammation, or its equivalent in plants, is not at present, I grant, so well understood as it is in higher animals, or as is the repair of a simple or traumatic injury in plants or in animals.

§ 8. In the study of gall-growth and of cecidia in general in plants, it has been found somewhat more easy than it

is in animals separately to consider: (1) the agents of injury; (2) the injury; (3) the irritant, or the agent of irritation; (4) the irritation; (5) the responses to irritation; (6) the reparative responses to a massive injury without irritation; (7) the etiology, extrinsic and intrinsic, of the characteristic responses to irritation, and of those to a simple massive injury; (8) the responding faculties, mechanisms, and the characteristics of each order of response—*i.e.* the simple reparative, and the damaging or inflammatory ones; (9) *Recovery* after the responses to irritation, as compared with the *Repair* of simple injuries, and its etiology.

I urge here, although it is not generally accepted by pathologists, that the responses to irritation in plants are strictly analogous to those which in man are held to represent a typical inflammation; yet it is not doubted by them that the reparative responses to a pure trauma or to a simple injury are in all essentials the same in both kingdoms of nature. So that we find in the process of repair the same terms are used for the responses in both kingdoms; and it is generally agreed that, as in essentials the process is the same, so the responding mechanism is always the same proliferating living cell in animals, as in plants; at least this is so accepted in all multicellulars: and even for unicellulars in either kingdom we are driven to conceive of a structural unit, somewhat less amenable to research, but which also responds by a proliferation, during a simple repair of injuries in them, and it cannot be absent in the proliferation of the cell, the higher structural unit, or the elementary organism, in the multicellulars.

It may be said that the nine heads given above collectively include most, I think all, of the essential points demanding attention in the study of the behaviour of

living organisms when exposed to injurious influences. It is very significant to remember, in reference to the main problems at issue, that plants are exceptionally convenient for this study in all the nine essential heads demanding attention, and of these I give here some examples.

§ 9. (1) *The agents of injury.*—In all the cases given here they are parasites, very often an insect. Take as an example *Biorhiza aptera*, plus the *Teras terminalis*, the life-history of which organisms has been so successfully studied that an intelligible conception can be formed as to their interests, the methods by which they are or may be forwarded, and the relations existing between them and the host plant. They are familiar to us as the causes of the common oak-apple. It is not intended to ignore the fact that the agent of injury can be, and often is, not parasitic in plants, but these are in some respects less instructive, and for the moment may stand over.

(2) *The injury.*—In this case, a wound across the whole axis of the winter bud of the oak, produced by the insect, *Biorhiza aptera*, or the agent of the injury, into which its ova are deposited; and as direct passive consequences thereof, death and decay of the wounded tissues and tissue elements, as well as of those separated parts functionally dependent upon the wounded axis.

There are at first no obvious vital responses, the nutritive functions of the plant being then at rest; but some slow and slight development of the embryos of the *Teras terminalis* in the deposited ova can then be observed. The injury exhibits well a common character of plant injuries, viz. a sharper line of demarcation between the injured and dead tissue elements, and the uninjured ones nearest to them, than is usually observed in animals when similarly injured.

(3) *The irritant.*—The agent of irritation, or that sub-

stance or influence which directly causes irritation. In the oak-apple, it, the irritant, is demonstrably related very intimately to the developing embryo *in ovo*, and apparently it is not any antecedent substance or influence. It is found to be concurrently operative—that is, it is persistent, and so produces irritation, and vital responses appear coincidently with the escape of the embryo from the egg, or it may possibly be a very brief period of time earlier; and the responses are also coincident or are concurrent with the commencement of normal growth in the host plant tissues near. Presumably, it is a material substance, in this case secreted by or separated from the parasitic embryo, and persisting in action during at least the earlier part of its embryonic growth and development only; but it is not the embryo itself. It is, however, possible that such an irritant substance, which has been at times spoken of as a virus, may have been formed in the parent, and may then have been contained within the egg until it is nearly hatched; but it is scarcely possible that it was deposited with the egg, and placed externally to it. In any case, the irritant substance or influence persists in action, or is repeatedly produced, for some time after the egg is hatched, and it is in its actions concurrent with the response; although there is no distinct indication, response, or manifestation of its presence before the hatching of the ovum begins.

In the galls common on willows, caused by various species of Nematus, the irritant is separable as a material substance of a slimy consistence and of a proteid composition. Beyerinck has shown that it is competent to produce or determine the beginning of growth of the galls, when deposited in a wound without an egg, although in these cases the gall is always smaller than the norm; and I have observed that an early death of an embryo *in ovo*

in these galls determines a similar arrest of growth of the gall, such as is also met with in numerous other galls; and this fact strengthens the opinion that the developing embryo *in ovo* is, if only indirectly, a contributing factor, in these galls, in the production of the irritant, and so of the responses it sets up.

In both the above examples the wound is an essential condition of the resulting responses, but it is not itself the irritant in either. The fact that, in the oak-apple, months pass over after the wound is made, and the deposition of the ova therein, before the characteristic vital proliferating responses begin, is explained adequately by the concurrent seasonal suspension of nutrition and growth in the plant, and not alone by the inactivity of the irritant then and there; while the prompt commencement of gall-growth in the Nematus galls after the wound is to be imputed to the coincident activity of normal nutrition and growth in the leaves, and of the acting irritant substance. Thus in both cases extrinsic and intrinsic influences are operative, concurrently, in producing the irritant and the vital responses.

The irritant substance observable in the Nematus galls may be, as Beyerinck suggests, a sort of growth-enzyme, or at least may contain one; but I have observed that it presents some quantitative relations to the mass of the gall, and I think it may act chemically, at least in part. It may be regarded as a provision in advance of the hatching of the eggs, fitted for the needs of the parasite, which demands very soon after the embryo escapes a large mass of food-material, seeing that it very early becomes a coarse and voracious feeder, which consumes much more material than it excites the growth of. The embryo *in ovo* in these galls, however, seems itself to exert some irritant influence, acting through the shell of the egg, and

thus co-operating with the separate irritant substance in producing the gall-growth. The irritant substance seen in these Nematus galls, unlike that which, as above said, is active in producing the oak-apple, is without doubt a product of the secretory activity of the parent parasite, and it is in this respect, I think, somewhat exceptional.

The fact that all the cynipidous galls are produced, so far as is yet known, without such a provision of an irritant substance in advance, and that, as their larvæ are very dainty feeders, and are not constructed for an early and free consumption of formed tissue, they are in no need of it, goes far to establish or at least strengthen the view that the deposition of the irritant substance with the egg is a special adaptation required for the parasite of the Nematus galls.

But a wound of tissue is not essential in gall-production, and it is not constant in all, however important it may be as a condition precedent in some, to enable the irritant substance or influence to come within a striking distance of the responding tissue units, which must always be susceptible to the irritant action.

Note, for example, the numerous galls induced by parasitic fungi, *e.g.* the well-known gall on the alpine rose and its allies, the common currant-gall on oak leaves, yielding the *Spathegaster baccarum*, the Bedeguar on the wild rose, and many others, which begin upon tissues the cells of which are at the beginning unwounded, so far as observation goes. The abnormally large and modified growths of hairs, known as erineums, due to the irritant actions of Phytopti, are in this respect also instructive, as they present no discoverable wound; but it is as yet uncertain whether the irritant, in these cases, is mechanical, physical, chemical, or fermentative; while it seems established that in some way the living Phytopti are the

bearers or producers of the irritant, probably at an early period of their life-history only ; and the actual irritant substance is not in these cases separable from the parasite in which it in some way inheres. The irritant, then, although it often cannot be distinctly separated from the parasitic agent of irritation in which it inheres, may be regarded as either a chemically active substance, or an enzyme, or a physical agent, such as heat, or a motion of some mode. It subserves in its effects the needs of the parasite, and it perturbs but does not kill the cells or structural units of the host.

§ 10. (4) *The irritation.*—This is only an inference ; but it rests firmly upon facts. Thus, it is shown that in the presence of the irritant, and in a definite relation to it, the living cells nearest proliferate even in excess and disorder, so as to damage the host organism, yet so as to be adapted in the result to the necessities of the parasite ; and as such cell-proliferations are measured in space and time by the activities of the irritant, the inference is justified that it determines them. Although no definitely observed changes have been as yet demonstrated in the living substance of the cells which then so proliferate, of a kind which can be imputed to the direct action of the irritant upon the living cell-substance, yet is some change in it, although as yet it is cryptic, a necessity of thought, as a condition precedent of the characteristic responses and cell-proliferations met with, bearing in mind the specific relations of the products to the parasitic organism. Such a cryptic change of the living substance of a cell, which injuriously modifies, but does not arrest, and often increases, its local vigour of growth and proliferation, is what I understand here by the term *Irritation.*

The word irritation is, however, so used in a technical

sense, one which has been much employed by many pathologists; but it differs somewhat in its meaning from that in which physiologists often use it.

It is a much more speculative question to approach when it is asked what hypothesis can be offered to explain the nature and characters of such a cryptic change in the living substance of the cell, the responding thing. I can on this point but suggest that it may be some mode of molecular change, of which the result is seen in a disordered local hyperplasia, with an abnormal and specific metaplasia. One is not without hope that the more minute study of the structure of the cell, considered as an elementary organism, which at this time is zealously pursued in the researches into mitosis and otherwise, may eventuate in clearing up some of the obscurity which now surrounds this question; but although it is not unlikely that some changes antecedent to an abnormal cell-division may be traceable in the structure of a cell, which do not evade observation by their minuteness, such as the parts of the nucleus or of the cytoplasm which can be seen to proliferate, sometimes, perhaps, during the period of irritation here thought of, it is scarcely to be expected that the more profound changes of the constitution of the living substances of the cell which are associated with a proliferation of physiological units or of their near equivalents will ever be amenable to direct observation; and, if this be so, the state spoken of as irritation will remain cryptic. The cryptic change, or irritation of the living cell-substance, may be manifested only by the structural unit or cell-proliferations, that is, by the vital reponses thereto.

It may be present either with or without a breach of continuity of the tissues near, or of the cell itself; and it is then, in the latter case, recognisable only by the near

resemblances of such responses to those pure repair reactions which so constantly attend a simple trauma ; yet always also with such characteristic differences as constantly attend the repair of a trauma, where it is attended by irritants in action, which are often parasites, or are related to them. So that, even when no irritant can be demonstrated, the characteristics of the responses may still suffice to prove that irritation is or was present.

In plant galls there is evidence enough to show that irritants in action determine the cells of the part to proliferate in local excess, and in an order of arrangement always more or less damaging to the host plant, though always presenting a *relation of fitness* to the irritant, either with or without any discoverable breach of continuity of the cells or of the tissues. In animals, such cell-proliferative manifestations of irritation are less generally accepted ; and at least in the higher forms of animals, the circulatory ones are more universally granted. The manifestations of irritation, that is, of the cryptic changes in the living substance of the responding cells, are thus thought of as indicating a stimulation of their evolved normal functions, of nutrition, growth and proliferation, and as demanding always an adequate supply of growth-materials, with the other requisite conditions of life ; but such stimulated or increased growth is always misdirected in a definite mode, determined by the irritant in action, which mode is open to observation, and it has been studied, I think, best in plant galls.

These manifestations of irritation thus include the conception of a stimulation of some of the normal faculties of cells or their components, especially of their formative faculties ; and in this sense no account is taken of any metaplasia or damaging changes in the said

manifestations, which are, however, also present. In perfect harmony with this view, it is found that the irritation, or cryptic change, in the living cell-substance, which misdirects the cell-proliferations, and is manifested thereby, is a minimum one, which leaves the proliferative powers still able to functionate even vigorously. It is thus economical, and as far as is consistent with the purposes of such change, in the interests of the irritant cause, it does not needlessly injure the host organism. It is essential to the idea of such irritation, that the cell irritated, and responding, must not be killed by it, however much it is modified.

Thus, for example, we find the tissues of a living, growing gall can and do repair some minor traumatic injuries, both normal and casual; and also they respond to other and different irritations in new directions determined by the different irritants, and for their benefit; and in various ways they often exhibit in their life-histories how economical and yet also profound is the change which had been determined in the constitution of the living cell-substance by the original irritation, by which its vigour of growth, though manifested in new modes, was left not destroyed, and apparently not diminished; indeed, often it seems locally increased, even if only for a short time. As an example may be taken the common willow-gall on *Salix alba*, due to *Nematus capreæ*, slight casual wounds of which often heal more or less perfectly; and it, like most, I think all, other growing galls, also repairs the normal wounds due to the expansions of growth, just as do normal tissues, even if the new tissue differs somewhat, but yet it is efficient.

As an example of the effects of an interfering new irritant, one may take the results of the attacks of lodgers or inquilines, as they are called, usually species

of a Synergus, as may be seen very well in the common currant-gall of the oak leaf, which yields the *Spathegaster baccarum*, or perhaps better still in the globular galls on the wild rose leaves, which yield the *Rhodites eglanteriæ*. The original gall-producer larva is in each such case killed very early in its life by the Synergi, which afterwards irritate the internal tissues of the gall in a different mode, and induce a different response or cell-proliferation, so that new galls within a gall result ; and these new galls show, in their structures and faculties, relations of fitness and adaptations to the Synergi, and are alike indifferent or damaging to the interests of the original gall-producer, or to the host plant. The *Spathegaster baccarum* galls so changed by the Synergi have a very different structure from that of the original gall, and maintain life and active growth for more than twice the period usual with a similar gall not so changed, yet always so as to benefit the invading Synergus, whatever may befall the original gall-producer, and always so as to damage the host plant, if only it may be to a minimum extent.

The globular rose-leaf galls yielding the *Rhodites eglanteriæ* in some ways are still better examples in which one may study the process of the production of new galls within the original one. The Synergi kill the gall-producer very early, and as entomophagous parasites consume its substance ; they then become phytophagous, consume as much of the food-layer of the gall present as is for them appropriate, disperse somewhat in the so enlarged chamber, and then begin to act as local irritants, excite a new, locally excessive, and specific cell-proliferation of the inner face of the chamber, by which they are each separately encapsuled, and within which capsules they each feed and develop, having produced responses which adapt the new gall to their own wants, so that it

presents relations of fitness to them. The responses so evoked are manifestations of the changes of irritation which each free and young larva of a Synergus determines; which changes, although cryptic, may well be accepted as themselves not less specific to the Synergus, than are the cell-proliferations by which they are manifested. The series of events presented to us in the growth of these new Synergus-produced galls are all very much determined by the young distributed larvæ after they are hatched and when they live a free life; they are not, at least in the later stages, due to the ova or unhatched embryos, or to a virus deposited by the parent Synergus; and the primary gall-producer has long been dead.

Certainly many, probably all, cecidia in plants show that the tissue units which respond to irritation, although economically, are yet very profoundly modified, but retain also, sometimes in a very high degree, proliferative faculties, such as may sometimes enable them even to revert in the direction of a norm, if not to reach it, as well as to react to a different irritant in the direction which it demands. One example of this is seen in the common nut-gall of the oak, due to the *Cynips kollari*, which begins in the axil of a very young bud, and the unwounded cells of which, in contact with the unhatched egg, with its contained developing embryo, grow into a specific gall the season before that in which they would develop if not so irritated. Such a proleptic growth is not uncommon as a consequence of irritation.

Another even better example of the profundity of the changes produced in the living substance of the tissue units by the irritants, is seen in those numerous galls which have a life-period longer than that of the plant-organ from the tissue units of which they spring: as in

the common larger vein-gall of the oak leaf, which yields the *Dryophanta folii*, and the oak-leaf spangles especially, which yield species of Neuroterus. In these cases such increased duration of life of the gall-tissues serves the interests of the gall-producer, and in no way those of the host plant; but they indicate very well the profundity of the irritation.

Still another excellent example is seen in the various galls in the anthers of oak catkins, which yield species of Andricus. When not the seat of these specific irritations, the anthers and the whole catkin wither and fall early; but when the galls grow in them the anthers, as modified, live much longer, and the rachis which bears them simultaneously lives and grows to abnormally large dimensions. Here again, all the responses are advantageous, or even necessary, to the irritant which induces them, and are only in a minimum degree harmful to the host plant. However, in this case only the anther gall itself is to be regarded as directly due to the specific irritation of the cells; while the hypertrophy of the rachis is to be thought of as due to the intrinsic relations of dependence of the host tissues, normal and abnormal, upon each other, and so is only indirectly due to the irritation.

There is also an instructive group of examples which shows another side of the picture. Thus, in the currant-gall on oak leaves yielding *Spathegaster baccarum*, the gall ceases to grow in size early in the development of the gall-producer, is apparently quiescent while this is in the pupa stage, and soon after the imago escapes by gnawing out a passage, the gall withers and dies promptly, while the leaf which bears it has yet some long time of vegetative activity before it. As has been noted, this series of events is changed when these galls

are attacked by Synergi, for then the Synergi-infested galls live as long as do the leaves. In each case, the interests and necessities of the gall-producer, or of the inquiline Synergus, determine the characters and duration in life of the gall-tissues produced, or those in which the irritation is manifested.

Quite comparable events are traceable in the oak-apple ; and in all the cases of this order the host plant is damaged so much as, and no more than, the interests of the parasite demand, the irritation being thus economical.

The profundity of the cryptic change, *i.e.* of the irritation in the living cell-substance, is seen also in the marked specific characters and relations of the galls produced in each case to the irritant, or to the parasite in which it inheres, and which produced it.

Thus, the common spangles on oak leaves may be found of three or even four species on the same leaf at the same time, springing from the same procambial tissues of the small veins, in a wound of which different species of Spathegaster have laid an egg, each producing a gall specific to it, from each of which comes a different species of Neuroterus, to which the gall-structure produced shows relations of fitness, or is adapted to it throughout its whole life-period ; showing thus that the specific qualities and characters of the gall depend upon the specific irritations produced by the irritant, and not so much upon the intrinsic attributes of the tissues affected, however essential these must be as factors in the process of gall-production.

Such a specific relation between the irritant and the responses which follow irritation is constant in other plant galls and cecidia, although not commonly quite so well shown as it is in the spangles.

The intrinsic faculties of the tissues and their units

subjected to irritation do, however, in some important, but in a less obvious, degree influence the characters of the responses thereto; yet not so as to obscure the specific characters, for these are mainly determined by the extrinsic cause or irritant. This truth is shown very well in the cases, sometimes met with, in which the egg has been accidentally misplaced by the parasitic parent; as when the currant-gall of the oak leaf grows upon a petiole, or on the rachis of a catkin, instead of, as is usual, upon the lamina of a leaf. Then, it exhibits distinct though slight corresponding differences of texture, always distinctly recognisable, and always so related to the gall-producer in structure and in faculties as to show relations of fitness to it.

Even more clearly the same lesson is taught by the occasionally misplaced galls yielding *Andricus curvator*, especially when they are met with upon very young axes, which then often become distorted, and may so remain for many years, apparently living and well, but as deformed organs, or axes.

The Nematus galls on willow leaves are good examples both of the profundity of the change in the living cell-substance, the irritation, and of the economy of such change, by which the proliferative and reparative attributes are so conserved that the tissues of these galls can and do repair some normal and casual external injuries, and can even approach towards a reversion to the norm. Thus, the common oblong galls found on leaves of *Salix alba*, due to *Nematus capreæ*, if not so much eaten out by the larva as to be incapable of maintaining life, and if not so immature as to possess too small a store of growth-materials, and are not dwarfs, live and functionate, in some of these essentials, even long after the larva has escaped, either when on still attached leaves, on naturally

fallen ones, or on quite small portions of leaves experimentally separated, when cultivated on damp sand; and they can then both grow some little in size, and exhibit some slight regenerative activity of the gall-tissues, as such, long after the leaf has decayed.

Such vital actions or responses are very autonomous; they are products of regenerative proliferations, but are apparently never quite like those of a normal leaf-tissue; and obviously they are not related to the gall-producer in any direct manner, or to the irritant substance which had been deposited in the wound with the egg, for by this time it must have ceased to be, or to the host plant, and they can only be imputed to the persistence, by a sort of inertia of motion, of the profound cryptic change or irritation which had been determined in the living cell-substance by and for the irritant; and this idea may help to explain the fact that the tissues so regenerated seem to resemble in essentials the gall-tissues, rather than the normal leaf-tissues; so that the result is not a true reversion.

Such detached galls seem to resist decay much more than do the leaves, and even more than do equal masses of an axis of the same plant under like conditions.

These galls so cultivated seem also to increase a little their chlorophyll, and to enlarge somewhat in dimensions; but they are not known to produce roots or buds.

Such vital actions cannot be regarded as true or direct responses to irritation, but rather as waning, almost regressive movements, comparable rather with those of a detached segment of cytoplasm from an amœba. They are still, as to their direction, influenced somewhat by the intrinsic attributes of the part, and also somewhat, though indirectly, by the specific characters of the irritation; but they are no longer needed by the irritant agent, and do

not any longer serve it or confer any benefit on the host plant. They are indications only that the tissues and their units are not yet dead, though dying, and that the irritation had economically spared their nutritive and regenerative faculties, and perhaps had even somewhat increased them locally—an opinion which, if somewhat difficult of acceptance, is I think tenable.

They attest the economy of the change in the irritation, and also the tenacity of the intrinsic normal reparative faculties.

Another of these Nematus galls, easily known by its spherical form and lenticellate surface, formed on the under face of the leaves of *Salix purpurea*, and caused by *Nematus viminalis*, illustrates better still, in some respects, both these features of the profundity and the economy of the irritation changes in the cell-substance, as well as the autonomy of growth of the gall, and the specific characters of its structures, adapted originally to the parasite, and yet due to the initial cryptic changes in the constitution of the cell, called here irritation.

When cultivated on small segments of leaves, or even as detached galls, they exhibit the economy of the changes in the cell-substance due to the irritation, by the vigour of their regenerative activities, and particularly by the length of time these endure. Excepting those of the galls which have been too freely eaten out by the gall-producer larva, and the immature young ones, and the abnormal dwarfs, many of them, under suitable conditions of cultivation, live and grow for periods of time much longer than do the organs of the plant which bear them, and even than do portions of an axis of the same plant of similar dimensions under like conditions. I have found some of them thus live for two winters and one summer after maturity. During this time, they seem to

increase somewhat in size and in greenness of colour, but they present rather less distinct evidence of a repair of casual external wounds, than do the oblong galls of *Salix alba*.

Often, however, as Beyerinck first observed, they emit rootlets of a perfectly normal structure, which may functionate freely, at least for a time; but as yet no one has observed buds and shoots arise from them.

This long-enduring autonomous life of the gall after it is separated from the plant, and after all similar masses of the plant have decayed, is as entirely without any direct relation of fitness to the gall-producer as it is to the host plant. It benefits neither, and it is met with in galls from which the larva has escaped, or in those which still contain a living one (if it be not then too freely consuming growth-materials), in galls yet attached to the leaves on the branch, or on fallen leaves. But it only appears when the conditions of root-growth, especially warmth and moisture, are supplied, that is, under good cultivation conditions.

The vital actions thus exhibited must be imputed ultimately to the evolved intrinsic reparative attributes of the tissue units of the plant; and they are much more closely related as to their characters, at this stage, to the host plant, than to the irritant substance, which in this gall, it will be remembered, as in the oblong galls on *Salix alba*, is separable from the parasitic agent of injury which produced it, and from the injury, as a slimy proteid mass, virus, or enzyme; but which, it can scarcely be doubted, is at this stage exhausted, and has itself thus as little to do directly with these cell and tissue proliferations as has the escaped larva.

So far, the cell-proliferations seen in these cases are those resembling repair, or tissue regenerations; they

seem to be also very much like the gall-tissue, but not the leaf-tissues ; and so, etiologially, they are complex. But the growth of rootlets of a perfectly normal structure, and functionally competent, for a time at least, represents actions of a very different kind, more akin to the normal plant attributes, and yet not quite like those possessed by the part of the plant from which the gall grew ; for the leaves of *S. purpurea* do not under any known conditions emit roots, although segments of their axes, if of considerable dimensions, do so freely. We may rightly refer these remarkable vital phenomena also, in so far as they are abnormal, indirectly to the irritations in the living cell-substance produced by the irritant, and persisting in the succession of cells and developed gall-tissues, by a habit of growth, or an inertia of motion, for an exceptionally long time ; and directly also to the evolved intrinsic reparative faculties of the host plant tissues, which gradually assert themselves, and at length attempt a reversion to the norm, yet always fail to effect this efficiently, so that the etiology is complex, and the response is the same. The tissue proliferative actions, which are in their results more like gall-tissue than leaf-tissue, show the less efficient attempts at such reversion, and are in part due to the initial irritation. The emission of roots, which are normal in structure and can functionate for a time, shows a rather more successful attempt to revert ; but it too fails of completeness, in that no buds are produced, and so the organism itself is not ever reproduced, and the result is not viable.

As in nature many of these galls fall to the ground with the leaves in the autumn, and sometimes emit roots then, while yet we find no young plants, so derived, near the old trees, it is clear that in this way new plants are not propagated. The suggestion that these galls, by a

late propagation of plants, may benefit the plant species, and thus compensate for the damage done during the growth of the gall, is therefore unsupported. In fact, these galls do very little actual damage to the plant, or to its organs, by their growth on the leaves, and thus they serve the purposes of the parasite economically, or with a minimum of damage to the host.

As in the other Nematus galls, chlorophyll is produced in them freely, and also, without much doubt, starch and other materials of plant-growth; the economy of the change by the irritation in the protoplasmic constitution of the cell is thus again made very apparent.

The specific character of these as of other galls as a whole, in relation to the primary gall-producer, is sufficiently shown in their adaptations, in their relations of fitness to it, and by their constancy of form and structure, as well as by their life-histories in relation to the species of plant and its allies, or to the gall-producing Nematus.

Their autonomy of life, growth, and development is exhibited very well by and in these relations of fitness; but in this respect they are not exceptional, when compared with many other galls. It is in their remarkable tenacity of life, and in the length of the period during which they can exhibit attempts to repair their own tissues, or to regenerate tissues and organs, and to revert towards a normal structure, that they are exceptional, and it is on this ground mainly that I dwell on them here at such length.

This tenacity or autonomy of life is best explained, I think, by the theory of habit of growth, or inertia of movement, before mentioned, which is in harmony with the conception that the evolved proliferative faculties are intrinsic to, and normal in, the host plant or its tissue units, the cells; but later are modified, at least temporarily, by the

irritation, that is, by the cryptic changes in the protoplasmic or cell constitution. These cryptic changes themselves are manifested mainly by the excessive local cell-proliferations, so directed as to be fitly related to the gall-producer, but so as not to be more damaging to the host tissues than is absolutely needful for the parasite—being, in short, economical changes. But the peculiar tenacity of life shown by this gall-tissue must be held to have been in some way, even although indirectly, related primarily to the gall-producer, and at some early period of its life beneficial to it; for the degree of tenacity observed exceeds that of the normal plant-tissues. (Surely such autonomous new growths are within the category usually called tumours.)

The economy of these irritations in the cell-substance is also well exhibited in the result, that is, in the gall as a whole; and it is especially shown in the persistence of the cell-proliferations, and of the regenerative actions in the gall throughout the whole of its life. For even while the irritant agent lives and persists somewhat in action, and also after the irritant has ceased to act directly, a return towards a norm is sometimes seen, in an attempted reversion towards, but not quite to, a norm; as in the production of roots, and in the retention of some share of the evolved reparative faculties of the host organism, as in repair of wounds in the gall: so that in all these initiative changes economy thereof is exhibited.

That in root-production in these galls the reversion to a norm is not complete, and does not reproduce an organism, is, I hold, a fact which may be accepted; but in theory such a complete reversion is to be regarded, I think, as possible, if we conceive of the cell as a potential organism. That these galls do not in fact completely revert to a norm, I conceive to be due to the profundity

of the cryptic changes of irritation in the living cell-substance, which in the leaves of this plant does not normally possess a faculty of root-production, or of bud-production.

When, in other cecidia, especially of axes, and then only or mainly at their periphery, such a complete reversion seems to occur, and buds are formed, there is reason to think that the living cell-substance has been less profoundly changed or irritated; and it may be then that there has been no, or but little, enduring or repeating irritation.

The views here expressed as to irritation have only a hypothetical value, although founded upon proven facts, and reached by a legitimate use of the scientific imagination; but, seeing that between the irritant in action, which is an observed fact, and the proliferative responses, which are also observed facts, standing in an observed and specific relation to the irritant, some intermediate events are necessities of thought, these events, although not amenable to direct observation, can with much confidence be thought of as also real specific, and necessary. The hypothesis of irritation thus acquires almost the value of a theory of irritation, in which it is held to mean, some cryptic change in the living substance of a cell specifically related both to the irritant and to the resulting responses; and one which is the necessary and specific intermediary between the irritant action and the response it evokes as its manifestations. Such a cryptic change determines a succession of cell-proliferations, not beneficial to, and always in some degree damaging to, the responding organism, but always adapted to and beneficial to the irritant; and such responses are in a legitimate sense true degenerations, although progressive.

The continuance in life of the products of the responses, sometimes apparently for long periods of time, after the

irritant has ceased to act directly upon the living substance, although some of its effects may perhaps persist awhile, and act even possibly as an irritation in some degree, indicates an important distinction of these responses from those damaging ones due to the direct effects of irritant actions; for these responses may still persist and be efficient if no irritant is remaining active, though some slight remnant of previous irritation may persist; and during such a period they, the responses, represent apparently the intrinsic evolved activities in the cell-substance, such as are manifested when an irritation is in a waning phase, or they are closely related to those of repair.

It is another and not less important character of these cryptic changes or irritations, that they modify and *misdirect* the evolved intrinsic reparative proliferative attributes of the living cell-substance, but do not directly and necessarily diminish them, never destroy them directly; and usually, perhaps always, increase or stimulate them locally at least, for a time; so that, after the initial irritant actions have approximately ceased, and the phase of waning irritation is passed, the normal reparative attributes of the structural units and cells, which have never been destroyed, can return efficiently and make an attempt at reversion, so that at length recovery of a sort can take place.

The whole series of events is thus a terminable one in its nature, though not always so in fact, perhaps because of the too frequent persistence or recurrence of a succession of irritants in action. The misdirected responses resulting from the irritation, though vital phenomena, lead often in the course of the process to a necrosis—usually, perhaps always, of some of the products of the misdirected cell-proliferation; and only then can we

think of the events as resulting in a degeneration, in the sense in which this term is now so much used, which is not, I think, its proper or original meaning.

Irritation, then, is not, and cannot be, directly necrotic in its effects, yet is it regressive or degenerative in the sense of the term as I have used it already; but its manifestations—that is, its products, the responses—readily necrose, and in that sense it is indirectly degenerative, in the more common meaning of the term, in its tendencies; and hence, the products being much mixed, the two different things are very apt to be, and often are, confused. A new word is wanted, I think, to connote degenerations as now understood, in the sense of the abnormal changes in normally persisting tissue elements, which lead to necroses, without the necessary intervention of degenerations in the sense of misdirected vital responses; and this new word should be used so as to include both the acute and chronic forms of such degeneration, which may proceed at a velocity which prevents any true cell-proliferative responses; but it should not be used also for the degenerations in the sense which I have given above, which implies the persistence of such vital responses.

In the course of these comments on irritation I have said but little about the irritation itself, as I know so little; but I have said more about its effects or manifestations, because in this way only can its existence and its characters be at all intelligibly appreciated. If we so conceive of irritation as it is above attempted to be described, that is to say, as a cryptic, economic, yet profound change in the living cell-substance, specificially related to a parasite, through the irritant, and also specifically related to the proliferative responses it induces, by which it is characterised, measured, may be diagnosed, and which are fitly related to the irritant,—then may we fairly

conclude that such responses are the equivalents of inflammation in plants, and to some extent may justify the doctrine assumed in the address, and quoted at p. 2, that "the reactions of all living tissues to irritants are rightly considered as inflammations;" but only if it be also granted that the equivalents of inflammations do occur in plants, and so in all organisms. This assumption, however, is not yet generally accepted, and the conclusion is at this moment only of value for the particular responses here dealt with in plants, and not for other organisms, until and unless equivalent specific relations are shown to exist in all organisms, between irritations and the responses they evoke. A step in the argument is, however, thus gained, which must be further pursued, and at the same time the various kinds and degrees of irritation must be attempted to be traced.

§ 11. (5) *The responses to irritation.*—In gall-production these are almost solely manifested by cell-proliferations; and from their intimate relations to the irritation and to the irritant, it has been found convenient to speak of them already under the head of irritation. They show adaptations and relations of fitness to the irritant and to the parasite in which it inheres, such as justify the view that they are produced under its direction—are consequences, in short, of the irritation, and are, in fact, as regards the host organism, misdirected in such a manner as to do damage to it, as is shown in the local excess and disorder of the said cell-proliferations and developments, and in their indifference to the welfare of the host plants, the tissue elements of which present active vital phenomena of growth, proliferation, and development, although they are at the time and place the seats of irritation, as a necessary intermediary between the irritant actions and the vital responses or cell-pro-

liferations, which correspond to, manifest, and measure the irritation.

The irritant actions, and the irritation, are both to be thought of as always injurious to the plant organism; yet are they economically so, and the evolved reparative attributes of the plant are always carefully conserved, so that the responses can take place in virtue of these normal faculties, although they, *being misdirected*, themselves damage the host plant. The actions of the irritant, and therefore the irritations, have well-marked relations of time and place with the cell-proliferative responses they evoke, and so measure them, or, what comes to the same thing, are measured by them. The cell-proliferations which characterise and dominate in these responses to irritation are always, and necessarily, associated with an adequate supply of growth-materials, often in plants seen in a later development of fibro-vascular tissue.

§ 11*a*. (6) *Responses to massive injuries without irritation, or true Repair.*—These are also chiefly manifested as cell-proliferations, although in these, not less than in the responses to irritation, a due supply of growth-materials, and adequate conditions of growth, must necessarily be presupposed.

They are distinguishable from the responses to irritation in that they are not misdirected, are in fact directed, by the undisturbed evolved reparative faculties of the plant; and the products of the cell-proliferation with development are not in excess or disorder, do no damage to the plant, but benefit it in various modes, either by closing a gap, or by regenerating some tissue or organ of a permanent and useful kind, such as show adaptations and relations of fitness to the injured host organism or its part.

This is typical repair in plants; it always involves some cell and tissue regenerations, often also organ regeneration,

and sometimes it is associated with a reproduction of the organism. It is measured by the injury in time and place. It is often seen contiguous to a growing gall, yet quite easily distinguishable therefrom ; *e.g.* in the repair of the wound caused by the ovipositor in the base of the leaf-stalk, in the axil of which a young gall of *Cynips kollari* is found ; and also in a similar repair of the saw-cut made by the *Nematus viminalis* in the vein of the leaf of *Salix purpurea*. In each case the repair products are readily distinguishable from those of the responses to irritation which constitute the gall quite close by, in the fitness of their relations to the injured organism or its part.

§ 12. (7) *The etiology, extrinsic and intrinsic, of the damaging responses to irritation, and of the reparative ones to a simple massive injury.*—This has been very well studied in plants ; for the responses to irritation are in galls very characteristic, and are easily distinguishable from those to a simple injury, not only by their structures, but by their relations to their extrinsic and intrinsic causes. Thus, in the responses to irritation (which, be it remembered, may coexist with a massive injury or not, and may then be known chiefly by the characters of the responses) we find, whenever the irritant is known, that the responses are adapted to it, and show *relations of fitness* to it, but none such to the host organism ; rather, always present some adverse or damaging ones to it. These relations of fitness are shown only to the *extrinsic cause of irritation* ; but as all the responses of either order necessarily involve the persistence in life and activity of the *intrinsic reparative faculties* of the organism, and indeed primarily rest upon them, the characters of the responses to irritation also show some necessary relations to these, the *intrinsic factors in the causes* ; although these do not dominate the specific direction and course of development of the products,

which therefore are not fitly related to the responding organism or its part.

Such relations to the intrinsic factors in the causes of the gall-growth, even in the responses to irritation, are seen, as to their quantity, in the dependence of the gall, as to its mass, upon the vigour of growth of the plant, or the organ thereof affected ; and as to their quality, in the minor differences of structure often visible when the galls spring from unusual positions upon the plant, an occurrence met with occasionally, and due to mistakes made by the parasitic insect in depositing the egg. But the product does not even then show such relations of fitness to the host organism as it does to the irritant.

The influence of the intrinsic causal factors upon the characters and structure of a gall is also seen obviously and frequently at the outer border of a gall, where often the resulting responses are less misdirected, having been less irritated, and may then even present slight but yet perceptible relations of fitness to the host organism, as is often seen in the *Andricus curvator* gall on the oak, or in the gall of *A. inflator*. However, these real and fundamental dependences of gall-growth upon the intrinsic causal factors notwithstanding, galls and all other cecidia in a very important degree show a predominant specific influence of the extrinsic factor, of such a kind as justifies one in speaking of the irritant as directing or as misdirecting the responses to irritation along lines of growth, cell-proliferation and development, which serve to adapt the product or response to the irritant, and thus mainly help to determine its varieties, characteristic structure, course and fate, without much apparent reference to the ulterior interests of the organism affected or of its part.

This care for the interests of the parasitic organism or irritant is often extended so far as to provide in advance

for the continuance of the parasitic species, by special structural adaptations for the dispersal of its progeny by the affected host organism; and if the parasitic organism be not by its own powers able to secure its own escape from its temporary prison and home, the plant often provides the means, to its own detriment, or that of its successors, for the dispersal of the germs of the foe at the proper stage of its development.

Examples of this are numerous. One very pretty one is seen in the galls of *Galium aparine*, caused by the *Cecidomya aparine*; another in some galls on the leaves of beeches, caused by *Hormomya fagi*; and others also in various galls on poplars, elms, and firs, due to some apterous insects. Some of these were known to Réaumur and to Malpighi.

The numerous galls caused by Phytopti are usually from the first open for the escape of the irritant; but when not so, some provision for its escape is found to take place in the gall at the time when the interests of the parasite demand it.

No such special provision for the dispersal of the parasite is provided in advance by the host plant, where, as is the case in the Cynipidæ, the enclosed parasite has itself developed organs by which it can secure its own escape and the dispersal of its progeny.

In plant-galls, especially, there is well shown the close relation which in all established parasites necessarily exists between the parasite and the responses evoked by it in the host, such as may enable the parasite to survive. Were adequate relations of fitness between the parasite and the host not existent, the former could not be established; and this is so for the whole of its life-cycle as a parasite in that host, both during its early and in its late stages, which demand that its progeny should develop and disperse. Thus, relations of fitness between a

parasite and the responses which it calls forth in the host are necessary for it, although not so, but damaging for the host in some degree, and they are specific.

Many of the facts upon which this general theory rests have long been known, although I do not think that they have hitherto been very fully set forth; and in any case this theory does not seem to be generally accepted, or at least applied, in regard to parasitism in animals. Lacaze-Duthiers (1853) (*Annales des Sciences Naturelles*) attempted to classify galls and other cecidia in accordance with their anatomical structures, as exhibiting adaptations, and *relations of fitness* to the parasite. His terminology shows this, as often, although not always, he names the layers of cells in a gall or other cecidium from their real or supposed values to the parasite. Some of his terms are still in common use—for example, "food-layer," "protective layer"; and they imply that the parts of the gall so named functionate for the advantage of the parasite. Even earlier observers, as Réaumur, Malpighi, and perhaps Redi, had observed some of these relations. Advancing and more detailed knowledge, both of the life-history of the parasite and of the development and fate of the galls, has, however, since the time of Lacaze-Duthiers added strength to the position he then took up, and increased very much the evidence for the view, that the parasite is the architect of its own house, even although the host plant is the builder. It may now confidently be said, that the irritated plant-tissue elements provide a suitable seed-bed and incubator for the germ or egg of the parasite, secure its safe hatching, nurse its embryo, feed, house, and protect its developing larva against harm in all its stages, and at length, by the development out of its own elements of a delicate specially adapted mechanism, often provides for the dispersal of the progeny of the foe, at the moment when it is ready, so that future

generations of the parasite may survive, even although those of the host thereby suffer. Such apparent altruism is surely only to be explained by compulsion.

In such a series of phenomena the intrinsic reparative faculties of the host are doubtless quite essential, and they build the gall ; but the erection shows, in its structure, proofs that the architect was an extrinsic factor, the irritant, the gall-producer, and the relations of fitness found are the proofs of this. The building of the gall under the misdirection of the parasite, doubtless has to overcome the resistances presented by the normal tendencies of the tissues of the host to persist in their habitual lines ; and these resistances may even justify the conception of a struggle against the irritant by the tissues of the organism ; but the preponderating directive influence of the irritant is so obvious and overwhelming, that the resulting gall-growth cannot with any justification be considered as representing the result of such a resistance to, or of a struggle against, the irritant. Rather it can more intelligibly be regarded as an excessive misdirected, even specific, response, in which the irritant is the extrinsic cause of the excess and the misdirection ; and while it uses for its own purposes the normal intrinsic reparative faculties of the plant or of its tissue elements, fails almost entirely to maintain them in their normal lines and directions, in face of the preponderating directive or misdirecting influence of the irritant which determines the species or the variety of the response. How relatively insignificant in its effect on the specific characters of the product this struggle against the irritant alone is, can be seen in the structures, adaptations, and relations of fitness to the irritant which the gall itself presents.

In galls and in other cecidia there is thus evidence that the tissues of the host, although so directed or misdirected

in their growth by the extrinsic irritant as to make them suffice for its needs, are not more perturbed by it than is just sufficient for this purpose; and the interests of the host are thus just so much conserved as is consistent with the needs of the irritant; and this fact also shows the economy of the cryptic change in the irritation.

So considered, the gall grows for the common advantage of both host and parasite, although the advantage to the former is but the economy of the change; while the advantage to the latter is essential and necessary to its being. The result is the striking and essential one, that the gall grows and lives as a consequence of the economy in the cryptic change, or irritation, produced by the irritant; but yet it so grows in a specific structure, and lives so as to serve the needs of the parasite at the cost of the host.

In many typical galls, not only the initial characters of their life, growth, and development, but their later fates and durations, are largely determined by the extrinsic factor, the irritant; but if we observe the various galls and cecidia met with in nature, we find many in which the interests of the parasite and of its host conflict but very little; and then the product, although always sufficient to satisfy the needs of the former, damages those of the latter in but a very slight degree. Thus, an almost infinite series of minute gradations occurs, between very heterologous and damaging true galls, and very slightly damaging cecidia (see, for example, some leaf-curls); and by these the gap is partly bridged over between the more typical and damaging responses to parasitic irritation, and the purely reparative ones to simple injuries without irritation; and one can easily connect in thought the intermediate parasitic irritations which perturb but slightly, with the non-parasitic irritations of any origin, extrinsic, intrinsic,

or both, and so partly fill the gap between them and the pure repair processes of response to a simple injury.

Plant galls present such conspicuous examples of the *relations of fitness* between the irritants, the extrinsic factors, in their etiology and the responses thereto, that it is excusable to deal with them here at some considerable length ; but it is by no means intended to say that all the responses to other irritations, which are often not parasitic, show equally well such *relations of fitness* between the responses to the irritation and the irritant ; while it is still held, that in all cases some such relations of fitness do obtain, even although they are more difficult to establish the proofs of in traumatic irritations than in the parasitic ones.

In the responses to a traumatic or a simple injury in plants, the relations seen between the causes or agents of injury and the effects are chiefly those of equality, and the fitness shown in them, is to the organism or the part of it which is injured, and responds as a pure repair, in virtue of its undisturbed evolved intrinsic reparative faculties, as set free, apparently by the injury. Thus the parasitic irritations, with the responses thereto, and the simple injuries, with the responses they evoke, as seen in plants, are well suited for the study of the etiology of both orders of response, that is, of the damaging and the truly reparative ones. The traumatic irritations, if persistent or repeated, are less well exhibited in their responses ; but they also show a like general result ; and in them also the effects measure the causes.

§ 13. (8) *The responding mechanisms and the characteristics of each order of response.*—The characters of the responses to irritation are such as in galls enable us easily to distinguish them from those to a simple injury ; so that by them each order of response can be referred to its causes,

whether simple injury or irritation, whether intrinsic or extrinsic. Yet are they in both orders alike in this, that they are manifested by cell-proliferation, with an adequate afflux of growth-materials to the part, though this latter is relatively much less obvious in plants than it is in vascular animals. This is well seen in tracing the development of galls from the gall-plasm, often an almost undifferentiated meristematic mass; and it is well seen in the very young oak-apple, in which the fibro-vascular bundles develop later than the time of complete inclusion of the earliest embryos by the gall-plasm. As has already been said, the distinctive characters of the two orders of response rest upon the direction or misdirection of such cell-proliferation and development, as is determined in the one case by the extrinsic irritant, and in the other by the normal intrinsic reparative attributes of the organism, when not perturbed or irritated; so that the characters are somewhat alike, yet differ.

The inference is obvious, I think certain, that the responding mechanism is the same for the two orders of response; and their distinctions are mainly due to differences in the direction of the process; so that in repair of a simple injury the injured organism or its part directs the succession of changes, and the product is fitted to it more or less perfectly, and is always beneficent to it; while in the responses to irritation, the irritants, or extrinsic causes, direct, or rather misdirect, the succession of changes for their own ends and advantages, without much regard to the interests of the organism, further than may coincide with its own, and on this ground do damage to it in the most economical way, and do so through and by the operation of the normal reparative powers as misdirected.

The products of these misdirected responses are, as I have said, more or less locally in excess and disorder in

regard to the host, cannot functionate adequately for it, and they live usually, if not always, for a shorter period than do the products of a response to a simple injury which are not in excess and disorder, and can then functionate for the injured organism or part adequately, so as sometimes even to reproduce it. The cases reported in which the products of responses to extrinsic irritation are said to have reproduced the organism are, I think, not well established; and the exceptional instances in which they functionate, as in some galls on willows, for long periods, show no benefit to the host organism affected. The fundamental responding mechanism common to both orders of response is the irritable living cell, the elementary organism.

The characters of the responses vary as do the conditions affecting the cell; and these conditions may be such as may modify its proliferations and developments, but must not arrest or destroy them. Different intrinsic reparative attributes of the cell or cell-complexes are also important factors influencing somewhat the characters of the responses of both orders.

§ 14. (9) *Recovery, after responses to irritation, compared with Repair of simple injuries.*—As the responses to a simple injury show a *relation of fitness* to the injured organism, and one of equality to the injury of it; and as the responses to irritant actions and irritation show a *relation of fitness* to the irritant only, with one of damage to the responding organism, without obvious equality in amount to the injury, if any be present, in a massive form; such responses to irritation must always antagonise the purely reparative responses to a simple injury so long as the irritation persists, and in the degree of its activity. As also the parasitic irritants, here dealt with as the best examples, in the normal course of their own life and

development, tend to cease or to change their irritant actions, the responses due thereto also then tend to vary or cease. Such responses to irritation, which, provisionally at least, I will now call the equivalents of inflammation in plants, are therefore in their nature terminable as the irritation tends to end.

When the developmental series of phenomena in the parasitic irritant ends, the nearest normal or approximately normal living tissue elements respond as in a simple repair as nearly as may be, and this necessarily, so that thus recovery of some sort begins and progresses. A condition is, however, still left to be dealt with in thought before recovery occurs; and that is the one of damage done to the organism, in part due, perhaps, to an initial massive injury if any had been, and in part due to the damaging responses to irritant actions, which may have been, indeed, the sole damages to be dealt with in the recovery, when the irritation has been produced without any initial massive injury, but not the less needing to be dealt with in recovery.

But it is expedient here to limit the use of the word recovery—a truly reparative process—to the repair of the damages of all kinds associated with the responses to irritation, and to separate it entirely from a repair proper of a simple injury, the process of which is not thus thought of as recovery, because it has not been previously associated with irritation, and the damaging responses it evokes. Recovery, however, so thought of, means a return, often a very gradual one, towards or even to the process of repair proper, in which the responses show in their results relations of fitness to the organism, or its part, and subserve its ends more or less perfectly, and it is possible only when the irritation has somehow relatively diminished or ceased, so as no longer to seriously antagonise normal repair. Then, recovery occurs necessarily, if the parts

of the organism are under normal life-conditions in other respects, and it does so then in virtue of the persistence of the evolved intrinsic faculties of nutrition and growth of structural units, cell-proliferation and development, in accordance with the attributes of the particular tissues of the organism involved, so long as their life endures; in short, because the automatic reparator, the cell, yet lives and functionates.

Such reparative responses, seen in recovery, are always very largely regenerations of tissue elements replacing those lost or seriously damaged—of course, with a due supply of growth-materials; and they are in plants also very frequently shown by or accompanied by reproductions of buds as potential organisms, much as in a true repair. It is less certainly known whether or no individual plant-cells, elementary organisms, after suffering the cryptic change spoken of as irritation, can and do themselves so revert to their normal states as to proliferate and develop along the lines and in the directions proper to them before they had been irritated; but there is, I think, a presumption somewhat in favour of the view that it is possible. This may be so in some cases, but the evidences for it are at present, I think, not quite adequate; and in any case, recovery in plants is less frequently shown by phenomena seeming to demand this explanation, than by those which indicate more clearly a replacement of a loss by a regeneration of tissue, due to a proliferation of the nearest cells, in which, so far as the evidence yet goes, either no such irritation had been present, or but very slight grades thereof.

Recovery, understood as reversion, is not perhaps so well shown or so easy to trace the processes of in plants as in animals; or perhaps it has not been studied with equal care. Paget was thus in one sense justified in

speaking of plants as showing examples of reparative processes less markedly than do higher animals; but I am not able to accept his conclusion that they present us with less evidence of their possession of the regenerative powers by which massive lesions, without irritation, are healed or repaired, and losses made good; and I think the evidence is rather the other way. Paget, in expressing these opinions, did not, I think, separate the idea of repair from that of recovery sufficiently, or not in the way above given, which indicates the close relationship, yet distinction, between the two ideas. In fact, plants do repair massive injuries, and show tissue regenerations very readily, if often less rapidly than higher animals do; but as they so readily also repair by reproducing new organs and potential organisms, and as this has not been very generally considered to be repair or a mode thereof, I think the completeness of the reparative powers of plants has been too much undervalued. That they are able somehow to recover after some irritations, and the damaging responses thereto, seems to be sufficiently certain; nor are facts altogether wanting to show how they do so.

However, in plant-galls or in cecidia of any kind we find no indications, such as have been so much insisted upon in animals, that during their responses to irritant actions, and by these responses, they themselves arrest the irritant actions or irritations, or appreciably hinder them; but rather, all such responses are found to be *fitly adapted to the requirements of the irritant*, so long as its stages of development are irritating. And although the products of these responses at a later period may be such as help towards the escape of the irritant, yet this phase is met with only when such escape is for the advantage of the irritant, or its progeny, at a time when it has almost or

quite ceased to act as an irritant, and has reached a stage of development demanding only freedom to disperse ; and in this way the responses do not conflict with the irritations or initiate recovery.

§ 14*a*. The arrest of irritation, as seen in galls and cecidia, is due mainly, if not solely, to the normal changes in the development of the irritant ; and it occurs when the interests of the parasite demand it. In no case known to me in plants is it due to the results of a successful struggle by the reacting tissues of the responding organism against the irritant, either by cancelling the irritation, or by expelling the irritant during the stages in which it acts as one.

However brought about, some such arrest of irritant actions is a necessary condition precedent for the efficient dominance of the reparative processes, which include recovery, and thus for such repair as often occurs of some of the various damages met with, *i.e.* for recovery after irritation or inflammation or its equivalent in plants. This would not be the case were it true that the responses to irritation are themselves reparative, or competent to arrest the actions of the irritant, or to cancel them, or were this their purpose. In short, the processes of recovery after gall-growth in plants are not parts of the responding process ; they occur only after the irritation has relatively or completely ceased ; and the responses do not themselves bring about such cessation in the plant galls ; and this is so whether we consider such responses as equivalents of inflammation in plants or not.

As examples of a sort of recovery after the damages attending and caused by the responses to irritation in plants, I may mention (*a*) those cecidia which are but very slight departures from normal states, such as are seen in some erineums due to Phytopti, *e.g.* those on the

leaves of alders, sycamores, and walnuts. We find then the hairs the chief seats of irritation, and of the responses thereto, in states of an active hyperplasia with a morbid metaplasia while the Phytopti are young, active, irritating, and apparently reproducing their kind; and about the time that these disperse and seek some other place more suitable to their then stages of development, the modified hairs wither and die. The lamina, however, from the under face of which the hairs had grown, had itself been modified, although in a much less degree, and had, although thickened a little and curved dorsally, retained its normal essential structures and attributes sufficiently, so as to both support the growth of the said enlarged hairs and to functionate for the advantage of the host plant almost normally. About the time when the Phytopti, the irritants, have dispersed, and the modified hairs have died, the slightly curved and thickened lamina persists in life, growth, and nutrition, and although it remains deformed somewhat, it appears to functionate fairly well, and to benefit the host organism only, of which it is a part.

In this series of events can be seen a sort of partial recovery, after the responses to irritation. The irritant has gone, the tissues which had been most irritated are dead, sometimes detached, and the nearer cells and tissues of the lamina which had been least or not at all irritated, yet had in some important degree contributed to the growth of the cecidium, and so had been a part of its structure, remain, and apparently *revert* to a normal state, or very nearly so—at least if they had been at all irritated.

It may be confidently inferred, that the cells of the lamina which thus apparently revert had been the seats of the cryptic change of their protoplasmic constitution, the irritation, so slightly, if at all, as to leave open for them a possibility of reversion, which was not the case

for the cells of the modified hairs, more irritated, because more closely connected with the irritant, and in the end they are necrosed as a consequence. Such a distinction between the more and the less irritated tissues and tissue elements, between the cells nearest to, and those further from, the irritant actions, is traceable in very many galls and cecidia, and is presumably in some degree common to almost all of them.

This example also shows well enough, that the reparative processes of recovery only then begin and go on, when the irritation has ceased, or very nearly so, and when the irritant has ceased to act, or has, as in this case, spontaneously departed; and when they take place, they are very like the normal processes of nutrition and growth; but in this case there is, so far as I know, no complete evidence of tissue regeneration of lost or dead parts, *i.e.* of the hairs, and the cell-proliferations seem only to go on in the normal way, in the curved lamina where the irritation had been least intense. There it is that recovery takes place, if at all; but it has there to revert only from a very slight distance, if from any.

One can only speculate, and that without any very sufficient grounds, on the extent and characters of the cryptic changes in the cell-substances which are less intense, and from which the cells can and perhaps do revert to or towards a normal state; compared with those in the cell-substance of the hairs which are so intense or grave as to lead to early death, and so to preclude repair or recovery at that part. It is legitimate, not the less, to note that the less intense changes are in the cells more distant from the irritant actions and nearest to the normal cells, because in these alone do any reparative responses proper, or recovery with some apparent reversion towards the norm, take place; and then they are shown in such a way, that

we cannot draw a sharp line of demarcation between quite normal tissue-cells, and those which had been so very slightly irritated that they can and do perhaps revert.

(*b*) A multitude of essentially similar instances can be found among leaf-curls due to Phytopti or to Aphides, or among the nipple-shaped phytoptous galls upon leaves of maple, sycamore, and alder, or among the purse-like galls due to Aphides upon the leaves of elms, and many other galls, in which it is a common factor that they are open for the gall-maker to escape, either from the first, or at a later period, if such escape is required for its needs; and such escape actually does take place.

I have already mentioned in another connection the galls, often produced by Diptera, or by some parasite not able to escape by its own exertions, yet needing dispersal, which, although closed during the main period of their growth and development, open by a sort of dehiscence, much as seed-capsules do, so as to enable the gall-producer or its progeny to escape, when its needs require it so to do. All these, in so far as they show any reparative responses such as we can rightly consider indicative of a recovery of any type, do so only after the gall-producer has ceased, or has almost ceased, to irritate; and then only in those parts of the gall or cecidium which are most remote from the action of the irritant, and presumably, therefore, had been less intensely or not at all irritated. In these cases, however, the reparative processes of recovery do not present us very conspicuously with any marked increase of cell-proliferation or development; and it is conceivably possible that in some of them recovery may be represented solely by a reversion towards the normal state of the slighter cryptic changes in the cell-substance, without any added cell-proliferations such as would rightly be called a tissue regeneration of lost parts;

but this point remains only a possibility, and is not at all established. It is to be borne in mind also, that recovery is not a constant result after the responses to irritation, and it may be absent, as will later on be shown, both for plants and animals.

(*c*) The broad facts above pointed to are also well seen in such a gall as that of *Andricus curvator*, which is found on the oak leaf and is composed as to its peripheral parts mainly of very slightly modified fibro-vascular bundles, in some excess and disorder of position and arrangement, and as to its inner portions, *i.e.* those which serve as the food-layer and the protective layer proper of the gall-producer, or those grown nearest to the irritant, is composed of plant-tissues much more modified by the irritation. That this inner portion separates from the outer, while yet the structural elements of both live, or at least are succulent, is apparently a consequence of a want of co-ordination of the growth of the two portions; and such separation occurs about the time at which the gall-producer larva becomes a pupa, and presumably then ceases to act as an irritant, although the lamina is at the time still expanding; and the peripheral portion of the gall then grows with the lamina, and apparently functionates no longer for the gall-producer's interests; but though it may be that it does not do so perfectly, yet it does in some degree serve for those of the host plant, without being at all adverse to the interests of the irritant.

Such a separation of an inner from an outer gall is a sort of dehiscence, and is associated with an early necrosis of the inner gall. Soon after this stage the pupa becomes an imago, eats a way out of the inner gall, and through the whole thickness of the outer gall; the former about this time withers and dies; but the latter persists in life and growth as long as does the leaf, or the other organ

which bears it. Such persistence in life of the outer gall implies doubtless some cell-growth and proliferation, a capacity to develop and functionate for the benefit of the host plant, and it is a sort of recovery by a patch. Although I have not verified the point by direct observation, I do not greatly doubt that, at or near the time of the separation of the inner gall from the outer, the latter produces near its inner face, where the surface-cells are seen withered and ruptured, a form of cork or other such scar-tissue, quite comparable to that common in the repair of a massive simple injury in plants. This is, then, a sort of recovery, imperfect though it be ; it takes place in the peripheral parts only, and only after irritation has relatively ceased ; and it is represented by some cell-proliferative phenomena, like those met with in a simple repair ; but it is not perfect, and its result is a compromise.

The instances in which, by a mistake of the parent insect in ovipositing, these galls grow upon or in a young axis, often show still better how permanent may be the tissue of the outer gall and how well it may functionate for the benefit of the host plant, although always it shows permanent traces of its origin in the deformity which results. I have met with examples of these deformed yet vigorously growing branches, of ten or twelve years old, in which I could still trace the persisting outer gall-tissues, limiting the cavity in which the inner gall had lain. The line of demarcation between the normal plant-tissues and the very slightly modified ones at the periphery, is in these and in many other galls not possible to be drawn. It is certain that the tissues are in close and continuous contact, and it is apparent that on both sides of the line the tissues can respond by cell-proliferations serviceable to the organism only after

irritation has ceased or has greatly diminished ; and this is a form of recovery.

(*a*) The galls which yield *Andricus inflator*, and are found in young developing oak shoots, also show a very similar series of events, in which an inner gall, composed of more modified structures, separates from the outer, composed of less modified ones. Such separation coincides in time approximately with the cessation of the irritation, and is accompanied by a necrosis of the periphery of the inner gall, but also by a growth and development of the peripheral parts of the outer gall, along apparently almost normal lines, in which, however, some deformity always remains. So that we find here also that recovery, though not at all perfect, does occur ; and here also, the parts which are most irritated and modified wither and ultimately die after separation, and the parts which are least irritated live and proliferate, and are continuous with quite normal parts, so as to show no observable line of demarcation.

From these galls at their outer limits, buds, apparently quite normal in character and faculty, are developed, although they usually are not quite normally placed in order of arrangement. The cessation of irritant actions is in each of these cases due to or coincident with the normal developmental changes in the irritant ; and in no single case is the response of a kind to hinder seriously, arrest, or cancel the irritant actions, or such as to interfere with its final dispersal ; so that there is no sign here given that these responses appreciably struggle with success against the irritant.

(*e*) The common *Spathegaster baccarum* gall on the young oak leaf also withers and dies as a mass soon after the insect escapes, and, the lamina being then still in a growing stage, I have reason for thinking it

delimits the dead and withered remnants by a sort of cork tissue continuous at one aspect with the dead gall remnants, and, at the other, with the cells of the living lamina; so that a sort of patch is thus effected, somewhat like that which follows a simple injury of the part, with some loss of tissue; and this is all that here stands for recovery. As has been noticed, this series of events is varied if this gall be infested with Synergi, when, under the influences which their young free larvæ exert, the gall grows differently, and then lives as long as does the leaf, or nearly so. In such a case no recovery of the leaf, a deciduous organ, can take place, for the two groups of irritant actions, and the responses thereto, persist as long as does the leaf; while in the same Spathegaster gall, when not infested by Synergi, recovery however imperfect is seen as a patch, the materials of which come from the nearer and almost or quite normal cells of the lamina. The influence of Synergi on the progress and fate of this gall shows well the dominant influence exerted by the irritant upon the specific characters of the responses.

(*f*) When a gall such as the oak-apple springs from an axis, and its whole mass withers and dies as an ultimate consequence of the series of changes attending the parasitism, from the deposit of the eggs to the escape of the mature insects, although the specific irritation has long before ceased; the dead mass often remains attached for long periods, it may be for years, and such attached dead terminals are dealt with then, as are many other dead tips of axes, by a production of scar-tissue, marking off the living tissues from the dead, and protecting the former, without, however, directly restoring the loss; always such scar-tissue is strictly limited in amount, and duly co-ordinated, never presents

cell-proliferation in excess and disorder specifically misdirected; so that the final result is very much like a repair by patch as of a simple injury. This is for such a case an imperfect recovery.

The collateral growth of other buds, such as is seen after pruning, and may be thought of as due to a liberation of growth, or to a restricted competition, may be left out of count in this consideration, as it does not materially affect such recovery as is here under consideration.

In each of these instances — and they but a few examples of multitudes of known varieties—there has been some necrosis produced, as an indirect consequence of the irritation and of the responses thereto; and it is produced frequently, in part by the directly destructive actions of the parasite at some periods of its life-history, and in part by the indirect effects of the disorder in the responding parts.

§ 14*b*. Recovery, then, signifies that irritation has relatively or entirely ceased, without saying how, or why, and that it is a delayed repair, as of a simple injury, which effects the best compromise possible. In so doing it has to deal with injuries and damages of different origins; and it can only make use of the evolved intrinsic reparative attributes of the cells and tissues of the part, either those which had been so little irritated that they are perhaps able to revert to a norm, or those which had not been at all irritated; for the more intensely irritated parts at length die.

So far, it has not been distinctly shown here that any irritations, with the responses thereto, are unattended by some necrosis at some period; nor has it been clearly shown that, in the recovery which we are now treating of, the state of true irritation, after resulting in cell-

proliferative responses specifically excessive and disorderly, the irritated cells themselves ever truly revert, so as that the responses quite recover and restore the norm by a series of steps within the same cells and their living substance which had been so specifically irritated in a marked degree. And we meet with but dim indications of such a conceivably possible reversion of a previously irritated cell-substance to a normal state, only at the periphery of the focus, where the evidences of such irritation having been present are not very well marked, and where the cells which do efficiently take part in a repair or a recovery may possibly all have been normal as certainly some of them were; and in any case, if some of these cells had been irritated at all, and had responded as a result thereof, they had been less profoundly so than had the cells nearer to the centre of the focus, which alone suffer necrosis, if any there be.

A strong presumption, then, is made out in favour of the view, that irritation does not necessitate a necrosis of all the cells in a focus involved, at any period of the series of events; and it is, I think, probable that some slighter forms of responses to irritation may possibly revert towards a norm; while it is certain that the more intense forms of response result always ultimately in a necrosis of some of the cells; and it is also certain that irritation cannot at once and directly kill, for then no responses could follow.

(*g*) There are many galls which separate themselves from the host plants while both the gall and the host plant tissues are still living and proliferating; and these demand a few words of explanation, in connection with recovery. Such separation takes place by specifically modified and directed cell-proliferations and developments which ultimately benefit the parasite, and even are

necessary for its persistence in life; while they damage the host very little, if at all, and may possibly even save it from other injuries or risks thereof.

See, for example, the separation of the galls of *Aphillothrix gemmæ* from the developing oak bud, or of the galls of *Hormomya fagi* from the leaves of beeches, or of the galls of *Biorhiza renum* from the oak leaves in late summer. All these are allied to some forms of a recovery process, and are in some essentials forms in which the irritated tissues have been in part necrosed before the separation. They are cases of an injured and damaged part patched at a line of approaching separation, not forms of a restoration of lost tissue or organ by a reversion of the same cells. Always the irritation has previously diminished, if not ceased; and always the tissue elements which effect the patch are those which had been either very slightly or not at all irritated, and the result always benefits the host organism somewhat, even if it be, as it is, also necessary for the parasite.

Such a dehiscence as throws off a living gall from a yet living plant-organ, although it may perhaps be regarded as a mode of ejecting an injurious thing, so as to reduce as far as possible the injury it might otherwise occasion, is always determined by the essential and necessary interests of the parasite, as is seen when its whole life-history is studied. While the host plant derives only those advantages, which I have before spoken of as due to the economy of injury in irritation, always and necessarily associated with parasitism, and such advantages as are represented by the production of a tissue or surface apt to repair and often very small. Here we have a case of imperfect recovery by a patch formation, not by a restoration, and apparently without any appreciable reversion to a norm of the previously irritated cells; and

here also the responses to the irritant actions are not the agents by which the irritation is cancelled.

(*h*) Many ripe galls separate from the plant or its organ, apparently much after the manner in which deciduous leaves do, so that, although on both sides of the line of separation the tissues live and grow, at least in the earlier stages of the process, yet at a later stage, on one or the other side of the line, the cells and tissues cease to grow, absolutely or relatively; and in this way the actual separation is largely brought about by the withering and death of the part to be separated and often under the immediate influence of casual impacts. The dehiscence of many capsules is largely effected, at least in its later stages, by desiccation after the valves are dead; and a very similar series of events is seen in the dehiscence and separation of those galls which gape to let out the gall-producers.

In like manner, whole galls are often separated from the plants on which they grow, either when the gall ripens, withers and desiccates, and the nearer plant-tissues do not, or *vice versa*, *i.e.* when the gall lives and the plant-tissues wither and die. For an example, see the fall of the small spherical galls of *Rhodites eglanteriæ* from the still green leaves of the wild rose. In these cases the detachment of the gall, there is reason to think, is prepared for in advance by a definite and purposive cell-proliferation with development, such as that which prepares for the fall of the leaf, and the actual separation is usually determined by some casual mechanical impact, such as rain or wind. But the fall of the gall is always for the advantage of the gall-producer, not a direct effect of the struggle of the plant against it. In such a case, the same mechanism which prepares for the fall of the gall, also co-operates in the repair of the wound resulting,

and this patch is all that here stands for recovery; but as the leaf also soon after falls by a very similiar series of steps, such recovery is of very little significance to the plant, and in any case is of much less import to it than is the dehiscence of the gall of *Aphillothrix gemmæ* from the tip of an oak bud, in which case the tissues on each side of the line of separation persist in life for a shorter or longer period after the separation.

(*i*) When, as often happens in the *Dryophanta folii* galls on oak leaves, and especially in the spangles which yield species of Neuroterus, the gall lives and grows longer than does the leaf, the organ of the plant on which it has grown, there is no important question of repair or of recovery from the injuries or damages to the plant which are due to the gall or its producer. The repair of the wound due to the frequently antecedent fall of the leaf, if wound it can be called, has no relation to the gall, but it is a normal repair of a normal injury.

In such cases as we have here to deal with, we have examples of damaging responses to irritations without any proper subsequent recovery; because the irritant actions and the responses or consequences thereof, often due apparently to a sort of inertia of growth or of abnormal motions, persist in the gall longer than the tissues of the irritated organ normally live; although these tissues are not, as in so many other allied abnormal processes, shortened in their life-periods. Such irritations are in their ultimate consequences at least locally fatal, although the separated and fallen spangle may live for months for the benefit of the parasite.

§ 14*c*. Thus recovery after responses to irritation is not a constant, though a frequent event, and it is therefore not a character by which the responses to irritation can be distinguished. The frequent fall of spangles by a sort of

dehiscence before the leaf falls, does not impair the value of this inference. In such cases the line of separation seems to be between a living gall and a dying leaf-tissue; the actual leaf fall may occur later, but it is very soon after. The processes of growth and development taking place within the separated spangle, after this period, have no direct relation to the host plant, either of repair, recovery, or otherwise, and are of import to the irritant only; although that they do in fact occur, is very significant in connection with the question of the nature of the cryptic changes of cell-substance called irritation, and with the question of the significance of the cell as a potential organism.

In all these cases, either necrosis or its frequent equivalent, separation, or both, take place; and this may be either of the whole or of a part of the gall or cecidium; and it matters little for my question whether the gall separates, or is separated, while yet it is living, or after it is necrosed. In either case, recovery, if it occurs at all, is represented only by a sort of patch at the point of separation, with which patch the separated gall has no concern: and although the separated new growth may persist in life for a long time, and its cells may proliferate, the host plant has no direct concern with this, which is of import only to the irritant, the gall-producer. In none of these cases is any recovery proved to occur by a true reversion of the actual cell-substance which has been distinctly irritated to a perfectly normal state; and in most of them, such reparative patching as is observed, is derived from the nearest tissue elements which had either not been irritated, or only very slightly so. In some other instances, as has been said, the peripheral tissues which are apparently only very slightly irritated, if at all so, seem able to revert in the direction

of a norm; but these are then always in immediate contact with quite normal tissues, to which some important influences must be accorded.

So far then recovery, as shown in plant galls and in other cecidia, is not in its essentials clearly distinguishable from a simple repair of massive injuries: the only point left in some doubt being the reality or extent of the capacity to revert towards or to a norm, exhibited at or near the periphery of some galls; and this is seen only after the interests of the gall-producer have been in some way secured, whether the gall has necrosed, or has separated as a living mass.

Although I have spoken here at some length of separation of galls, or of necrosed parts of them, it must be remembered that not all of them do actually separate from the plant. Many remain continuous with it for years after their death and desiccation, as do dead extremities of axes; and then they are dealt with in a similar manner, that is, a layer of a sort of cork tissue intervenes between the dead and the living, and may serve to protect the host plant somewhat. Thus we have a reparative patch to represent an imperfect recovery, and one which, both in plants and animals, is in some degree comparable with what is known in the latter as encapsulating fibrosis, or a scar formation.

This result is due to a process essentially the same as that seen in a separation of some normal type; and it is a reparative one, resulting in an isolation of the useless. But there is no good evidence to show that during such a process any true reversion of any distinctly irritated cell-substance to a norm plays an important part. It is only a case of a repair by a compromise after irritation has relatively ceased, not of a recovery in which the products of response to irritation are themselves the

essential agents of repair or of recovery, or the means by which irritant actions are cancelled, separated, or annulled in any way. In no case is recovery, though a delayed repair, to be confused or mixed up with the responses to irritation, as is, I think, too often done.

§. 14*d* (*j*) Although, in another connection, the remarkable features of autonomy of growth seen in the Nematus galls on willows have been spoken of, they must be again here referred to in connection with recovery.

The growth of perfect roots from the Nematus galls of *S. purpurea*, under circumstances which show a complete independence of the gall-producer, and of the host plant, strongly indicates the remarkable autonomy of this gall; and, if in a less degree, also the attributes of the cell as a potential organism. Such productions of a normal organ from an abnormal mass of tissues which had certainly been very profoundly modified by irritation, also indicates with sufficient clearness and certainty the possibility of a reversion towards, and even possibly to, a norm of a previously irritated cell-substance. This is a most important fact, and one which at present stands very much alone. Such growth cannot, however, be regarded as an instance of a true recovery.

The process of the root-growth, reversion to a normal organ though it be, is not directed by, or of benefit to, the host organism; rather it presents us, in the result, with an example of what Loeb calls heteromorphism in animals, seeing that roots are not normally produced by the leaves of this plant; they are in this case wrongly placed, and they show no true relations of fitness either to parasite or host. The result is not a true recovery, nor even a compromise. Aberrant as such root-growths are, they do show that the cells of the gall have retained, with their proliferative faculties, in some degree a capacity for rever-

sion, in virtue of which, under conditions of cultivation favourable to root-growth from stem cuttings of the same plant, they can and do revert so far towards a normal whole plant, as to produce roots even more readily than do stem cuttings of equal bulk. On this ground they are of very great if indirect interest in regard to the question of recovery from the effects of irritation in plants, and, more than any other known example, show at least the possibility of a recovery by reversion in plants as distinguished from recovery by patch or replacement, such as is seen in a scar, grown from the nearest normal cells, or from the less distinctly irritated ones at the periphery of a gall. Such root-growth, however, only then occurs when the irritation has relatively ceased.

I know of no instance of recovery in plants, whether by reversion or by patch, without a previous complete, or at least considerable, cessation of irritant actions. I know of no instance of any recovery in which this cessation or great diminution of the irritation is brought about by the processes of response themselves, tending to cancel the actions of the irritant, or to expel it, and so to indicate that such processes represent a successful struggle by the tissues of the host plant against the irritant cause of the response, in which the host plant is the victor and the irritant the vanquished. Such cessation or diminution of irritation as is met with, appears always related to a stage of development, or to some inherent need of the parasite, and to be always in harmony with its interests.

Neither do the responses which the host tissues then show in a modified form, then or at the later stage, conflict with the interests of the parasite ; but rather they still harmonise therewith in this, the declining stage of irritation, as they did in the earlier growing phases, during the development of the gall and its producer ; and

although in these later stages the host plant is no longer seriously damaged by the responses, and in some cases may be benefited, and may even make provision in advance for a sort of imperfect recovery by a patch; yet is this last never adverse, and is often very beneficial, it may even be essential, to the life of the parasitic species, as may be seen in the instances given of the dehiscence or of separation of living galls from living plant-organs.

Herein is well exhibited again the economy of the disturbance in the host organism which parasitism involves; in virtue of which, while it is necessary for the parasite that the host should live and the tissues of the part be able to proliferate, these latter are not more disturbed than is absolutely necessary to enable the parasite to live its life; and so, when the parasitic irritant has ceased its demands as such upon the host, the tissues of the latter can and sometimes do, either by a reversion of the less disturbed cells, or by a patch derived largely, perhaps chiefly, from the not disturbed cells, bring about what is called a recovery, although in many cases, when the needs of the parasite so demand, the host tissues are necrosed; and in that state they may also serve some of the purposes of the parasite in that locality.

In virtue of this same economy of disturbance or irritation of the living cell-substance, by which there is conserved for the host plant the possibility of a recovery of some sort and degree, in or near the focus, there occurs also the excessive, perverted, or perturbed cell-proliferations, directed or misdirected by the irritant so as to serve its needs, which characterise the responses seen in galls and in other cecidia; so that the intrinsic reparative proliferative faculties of the tissue elements are primarily the foundations and sources both of the damaging responses to irritation, and of the repair or recovery from

such damage, when it does occur, which it does in some degree frequently.

Hence, throughout the whole process of the damaging responses to irritation, however severe the damage may be, and however destructive the result may be to the part involved, the amount and intensity of the disturbance or irritation of the living cell-substance must always be such as does not directly destroy this faculty of cell-proliferation; indeed, it often increases it locally and temporarily, even when misdirecting it disastrously for the host plant, at the parts chiefly involved, which are then seats of an intense irritation and inflammation.

Recovery by a local reversion is in such cases unknown, and is, I think, impossible; although, when the galls end in a necrosis and a separation, recovery by patch may be met with, when the irritant, whether a parasite or not, is also somehow cancelled or separated, and apparently then for the mutual benefit of the host and the irritant.

§ 14*e*. (*k*) It is often otherwise, when such an irritant is present as a colony, and reproduces its kind in or so near to the focus involved as to reinfect and so to interfere with recovery by patch, the new local infection causing the damaging responding process to spread. As has been said, recovery is not a constant result after a plant organism has responded to irritation; for the irritation may, and often does, persist or recur during the whole period of the life of the plant or of the organ of it affected; and then the necessary condition precedent of recovery, that is to say, the relative cessation of irritation, is wanting.

Nevertheless, during even these irrecoverable and gravest forms of the responses to irritation, the fundamental intrinsic faculty of cell-proliferation persists so long as life lasts, and it must assert itself in some degree; and such normal attributes inherent in an organism, in its

origin and nature, are present as consequences of the economy of disturbance, or of irritation, which is a law of parasitism, and is needful to an established parasite, whether or no it be advantageous for the host. Nor is this truth in any degree impaired in its significance by the fact that, by the exertion of these normal faculties, under influences by which they are misdirected, even stimulated, no results occur which are materially advantageous to the host, and no recovery takes place either by reversion or patch, in a multitude of cases; that is to say, when such misdirection persists or is repeated or spreads, and is not cancelled by any causes, whether in the irritant, or in the host, or in neither.

The whole group of simply and purely destructive actions, as distinguished from the irritations, I leave here out of count; although gradations are met with between the two sets of actions, which would repay a careful study. I mean by destructive actions those which by their severity prevent any vital responses, proliferative or other —as, for example, when, by heat or by a chemically acting caustic, tissues are at once killed, whether dissolved or removed matters not. But such destructive actions, if local, and not in their own nature spreading, often, I think perhaps always, show at their outer limits some reparative proliferative responses, that is to say, where they are not fatal or destructive; and they may there be irritating for a narrow zone, outside of which even this change ceases, and effective repair then dominates there as a necessary consequence of the nutritive life of the part, just as in a case of a simple injury. See the margins of a wound caused by a coarsely feeding larva. But, where, as often happens, the destructive actions spread, and do so as fast as any vital responses can occur, then none can follow, and such cases have no place in the

consideration of a recovery of any kind, or of a repair, nor are they irritations.

There are, however, great groups of cases in which the agents of injury and of irritation multiply and spread so fast as to make recovery there and then impossible; yet, during such multiplication and spread, they may act temporarily, locally as irritants, give rise to cell-proliferative and other responses more or less obvious, the products of which often very soon decay and disintegrate, and never heal at the periphery of the focus, because the irritant actions there persist and spread, and lead to destruction too rapidly, even though indirectly. Such agents of rapidly spreading injury and irritation are often parasitic fungi or bacteria, and they may kill the whole organism, without ever reaching any distinct limiting line of tissue capable of an efficient repair, or of recovery; although they had produced some perturbed proliferative responses tending to early necrosis and disintegration.

Here, the irritant itself is only indirectly destructive, and the intermediary response is a proliferative reaction, but itself is very rapidly damaging, and, even if only indirectly, is destructive to the organism or its part; yet is it also due to the intrinsic normal reparative faculties of the same organism, as misdirected by the irritant and for its benefit; as in many cases is shown in plants by the beneficent results to it of such necrosis as often follows, to the progeny of the parasite by providing for its nutrition or dispersion.

Thus a fatal destructive result often follows irritation of the affected organism or its part, and no recovery of any form is possible under such conditions; although the process is one in which the reparative faculties of cell-proliferation and development had been throughout

operative, had indeed been the agents of destruction; the automatic reparator, that is to say, the cell, having been coerced into lines of action opposed to its own requirements, but demanded by those of the parasite.

If any responses to irritant actions can with propriety be spoken of as indications of a struggle of the organism against the irritant, which may perhaps be disputed or qualified, it cannot be doubted that such struggle fails utterly in these forms; and in the forms in which the irritant actions terminate somehow, and a recovery of one or other kind eventuates, it is not less certain that the termination of the irritant actions is not an effect of the responses in question, but takes place in accordance with the inherent requirements of the parasitic irritant by changes in it, and normal to it. So that in these cases the asserted struggle against the irritant is quite without beneficent effect to the organism. Rather must it be said that the responses to the irritant actions serve the irritant's interests, and so long as they endure almost ignore those of the responding organism, often operate to its serious damage; and only when the irritant actions cease, relatively or absolutely, can recovery take place of any type; nor then, unless some essential part of the affected organism remains outside of the whole process, and not seriously influenced by it.

In this sense *recovery*, when it occurs in plants, at least in galls, etc., is not a consequence of the asserted struggle against the irritant; rather it is a result of the cessation of the irritant actions, and of persisting normal intrinsic reparative powers then become dominant and no longer misdirected. Such a cessation of irritant actions, when it occurs, is due to causes irrespective of the reactions or responses here dealt with, and it is commonly due to a phase of a part of the life-history of the irritant.

§ 15. In this section I have dealt almost solely with the responses to irritation of parasitic origin, because they are more characteristic and instructive, and have therefore been studied with more definite results; but I do not for a moment doubt that non-parasitic agents of injury also can, and often do, if persistent or repeated, act as irritants, and then determine responses which are related to their extrinsic causes, very much as are those I have already spoken of; that is, the effects and causes measure each other.

Here, I need only add that, so far as I have been able to learn from observation and books, such traumatic or not parasitically caused responses are less strikingly specific in form and structure than are the responses to true parasitic irritations, show a much closer resemblance to the responses to a pure trauma, *i.e.* those seen in a simple repair, are sometimes less rigidly localised, and sometimes are so widely diffused in the responding organism as to approach somewhat to those changes of form and structure commonly considered as due to "habit of growth," or to the more diffused changes in the environment; suggesting, indeed, though not proving, a possible mode of origin of some varieties.

In this section I have also dealt with the three groups of accepted facts which involve *repair*, *inflammation* or its equivalent, and *recovery* in plants, and in so doing have under the nine heads given above included the essentials of all the important phenomena known in them, or, I think, in animals, in relation to the above three groups of accepted facts; and this will, I hope, be made more clear in the following section.

SECTION III

THE QUESTIONS ASKED, SIMILARLY SUBDIVIDED, STUDIED SO AS TO SHOW THE MUTUAL RELATIONS OF THE FACTORS INVOLVED, IN THE THREE GROUPS OF ACCEPTED FACTS, AND THEIR MANIFESTATIONS IN ANIMALS

§ 16. WITH objects in view similar to those which directed the previous section on plants, I will, on grounds of expediency, in dealing with animals postpone repair, and take prominently the series of changes known as inflammation in man, and at present I will assume a no more close analogy between them and the phenomena met with in plants, than such as may justify a careful comparison and study.

In so doing, it at once appears that all the nine heads under which the question of responses to injury and to irritation has been studied in plants, which collectively contain the essentials in them, are also presented to us in observing inflammation in its typical forms in man and in the higher animals; and it becomes needful to inquire how far they also contain its essentials in what is or may be accepted as inflammation in all animals, so as to ascertain in what animal organisms that process can be observed.

In typical inflammation, as seen in man and in the higher vertebrates, however, the phenomena are much more

complex than in plants, and they are in many respects more difficult to observe, to experiment upon and to explain, than are those of the responses to irritation seen in plants. Hence has resulted a great diversity of opinion, both as to the actual facts, in respect of their order and importance, and in regard to the theories by which they are attempted to be explained. Indeed, such diversity amounts to a chaotic confusion, and conflict of view so great as to have led some very competent pathologists to suggest the abandonment of the word and even of the idea of inflammation.

Thus Andral, in his preface to the *Précis d'Anatomie Pathologique* (1832), says that he has not described the complicated diseased condition called by authors inflammation, but has chosen rather to deal with the separated and yet connected disease-states it presents, and to avoid the use of the word inflammation altogether. He, in short, seems to give up altogether the inflammation idea as then it was accepted.

Thoma also, in 1886 (*Berl. Klin. Wochenschr.*), expressed the view that the inflammation idea under the then present conditions should be abandoned, because he despaired of the adoption of a definition; and yet thought one necessary, because the then existing idea he held to be so general and indefinite as to possess no real connection with facts, and because it included many disease phenomena, the ideas of which are derived from repeated analogies, and not from direct observations of facts.

These suggestions, however, have not so far received wide support, and as the phenomena in all cases remain, are important, and demand attention, they are not likely to be supported, unless the word, or the idea, or both, are supplanted by others more conformable with facts, and more harmonious views are thus formed.

Even Andral and Thoma themselves have not been able to avoid dealing with the phenomena which the inflammation idea includes, and their works show that some such idea has been necessarily present in their minds.

Notwithstanding these difficulties, however, the study of typical inflammation, which has been pursued since the dawn of history, and partly on account of its theoretical interest, has received so large an amount of attention from some of the ablest students of nature, that the results reached are of the utmost importance. It is not, I think, excusable to despair of our attaining some day to a consensus of opinion, in regard to the problems involved, as nearly general as is usually met with in respect of other comparable problems. The results already reached are indeed so promising and instructive, that not only the student of animal pathology, but also the phyto-pathologist, should feel obliged to take them into careful account, or else he will neglect an invaluable part of his own question.

This is so, both with regard to the observed facts, and to the theories by which they are attempted to be explained; and as some of both are in some ways different, in typical inflammation, from those which have been observed and taught in regard to the responses to irritation shown by plants, it is expedient here, in dealing with typical inflammation, to use a rather wide latitude and not to follow with too great strictness the lines suggested by the nine heads as exactly as I have done in plants, lest the comparison to be instituted between the responses to irritation in the two kingdoms of nature should not be quite a fair or judicial one.

§ 17. As has been said, all the essential facts included in the nine heads spoken of in regard to plants, are also found and are essential in typical inflammation in animals; but the theories by which they have been attempted to

be explained are very unlike; and in typical inflammation there are also some other facts met with, which are perhaps not so clearly included within the nine heads, or are not so clearly observed in plants; and the theories explanatory of the phenomena necessarily differ somewhat from those which have been suggested above in regard to plants, and they may even apparently conflict therewith.

This truth may help to explain the fact, that most zoo-pathologists who have treated of typical inflammation do not explicitly recognise any analogy between it and gall or cecidium growth in plants, and some have explicitly denied its existence. As, however, in animals not less than in plants, all the nine heads or essential subdivisions of the questions studied are met with, and in them also include a consideration of the phenomena as a whole, they must be here dealt with in a somewhat similar way.

It is an observed fact that in the highest animals:—

(1) *The agents of injury* are, or may be, the same as those met with in plants. They may be non-parasitic or parasitic. Among the former are found physical, mechanical and chemical ones, in the more obvious examples; and among the latter, with or without the non-parasitic agents, also some ferments, usually then among the less obvious instances of injury, thought of as massive. All of these have in human and in animal pathology received careful attention, and with such important and profitable results that the phyto-pathologist may not neglect them.

(2) *The injury* is also in essentials the same for each kingdom of nature, and in each it implies a solution of continuity or defect of tissue elements, or, in not massive injuries, perhaps only of units of structure. It is a passive effect of the action of the agent of injury. In higher animals it has been investigated more minutely, and perhaps with greater success in many respects, than

in plants, notwithstanding the greater complexity of the investigation, so that here again the phyto-pathologist has much to learn from the zoo-pathologist.

§ 18. (3) *The irritant*, or agent of irritation, has also been studied with great care and success in animals; and it is accepted as being often closely related to or produced by a non-parasitic or a parasitic agent of injury, in animals as in plants. Although the distinction is not always very clearly kept in view, the irritant is in both of them separated, at least in thought, from the agent of the injury and from the injury itself, which is therefore not held to be itself necessarily the irritant, in the sense of being a constant antecedent or concomitant of a typical inflammation; although it may be and often is so spoken of, in regard to some muscle, nerve, vascular and other vital responses.

Thus, the agent of injury may or may not itself be also an irritant, or an agent of irritation, in the sense of the term as here used; but, seeing that all the various agents of injury may and do sometimes so seem to act as irritants as to determine directly or indirectly what is known as inflammation in the higher animals, they are somewhat too generally accepted without much evidence as irritants in this sense; although their relation to irritants is not a constant or a necessary one, but is a casual one, often dependent upon degree and on intervening factors.

Then, the distinction is often drawn at the line of destruction; and in animals, as in plants, the truth stands, that where the agent of injury is destructive there is no vital response; and although immediately outside this limiting line pure repair or a regeneration takes place, if and when no truly irritant actions intervene, at this very zone or line we may meet with true irritant actions

due to or associated with the same agents of injury as elsewhere were destructive; but acting at their outer margins with less intensity, and apparently then as irritants. In this way may be derived the idea of the irritant as an injurious agent, not itself destructive of life in the tissue elements irritated, yet necessarily in some way or degree injurious to them, and as modifying them, in their course of life.

This conception of the irritant and of its action is the same for plants and animals; it is common to the parasitic, as well as to the non-parasitic, agents of injury or of irritant actions, and it is also complete in cases where there is no known agent of injury or any massive injury.

Put more shortly, it says any agent of injury which acts gently so as to injuriously modify but not destroy the vitality of tissue elements may be, or act also as, an irritant, and then the irritant stands in the same relation to irritation and its response, inflammation, as does the agent of massive injury to the injury itself and to its repair. This is equally so in plants and in animals, although the responses to the irritation in the former are not as yet generally accepted as inflammation, or even as an equivalent thereof.

The study of the non-parasitic irritants has, I think, been more carefully and perhaps successfully followed in animals than in plants; and in any case we have a greater mass of valuable facts accumulated in regard to them; so that we know somewhat more of the nature and effects of the various physical and mechanical injurious influences, and of the chemical substances operative in the production of typical inflammation in animals so set up, than we do of non-parasitic irritant injurious influences or substances in plants, or of the responses they evoke.

See, for example, the effects in experimental research of

the application to a responding tissue of moderate heat, mechanical impacts, and some substances like mustard or iodine or croton oil, in which the agent of irritant action does not produce an obvious injury so long as it is feeble in its action or brief in its duration. Thus is given, not in thought only, but in objective fact, the irritant, distinct from the agent of injury or the injury itself.

It is otherwise in respect of parasitic irritants, at least microscopic ones, which until the last quarter of a century have received a smaller share of attention from zoo-pathologists than have non-parasitic ones. And even now, although almost daily new illustrations of the great importance of microbic irritants in higher animals are brought forward, there seems to exist in the minds of many pathologists a disposition to look upon non-parasitic irritants as the more important and more instructive, or at least to retain them as types for the experimental study of the responses.

Since the labours and discoveries of Pasteur, Koch and Lister, however, there has been a very marked change in this respect; so that more attention is now given to microbic parasitic irritants, and comparatively less to non-parasitic ones, than formerly was the case, and in this way etiology has been much advanced and practice improved. But bacteriology, as studied in animals, does not quite so well enable us to view the question from the standpoint of the irritant parasite, as does the study of galls in plants due to higher and more complex parasitic organisms; because, perhaps, we know so much less of the life-history of the bacteria than we do of the Cynipidæ, for example; and also because the responses or results of the irritation produced by colonies of minute parasitic organisms show in many respects less definitely relations of fitness to the irritant, although they do of the reverse

to the host, than plant galls do to the irritation of the gall-producer.

Hence, although in the higher animals in which chiefly typical inflammation has been studied, it is now generally conceded that some pathogenic microbes intervene when a simple wound is followed by the series of changes so named, and that they are then irritants or contain them, yet are they very commonly then thought of as important factors only, and not as the sole irritants, or at least they are less positively so considered than are the gall-producers, and apparently in large part because the results do not exhibit in the same degree characters fitly related to, and specific to the irritant, or at least not obviously so, in the majority of the cases.

The factors in the responding processes, which in these cases are sometimes closely related to the non-parasitic agents of massive injury attending or preceding the inflammation, being often thought of as of more relative importance in animals than they are in the corresponding cases of plant-injuries and irritations, and the responses thereto ; and the irritant being thus held to be derived from or due to the non-parasitic as well as the parasitic sources, or to both combined, as indeed sometimes may be the truth, a conclusion is reached which diverges in many particulars in regard to the parasitic and the non-parasitic irritant actions, or to the mixed cases, both in animals and and in plants.

In these cases in animals, however, it should be observed that the parasitic organism, although closely or even constantly associated with an irritant, is not always clearly shown in its real relations thereto, and the irritant influence or substance is not often so clearly separated therefrom, as it is, say, in plants, in the case of the willow galls especially ; nor is it so clearly discernible separately, as in

the cases in which the non-parasitic agents of injury become irritants at the periphery of the often destructive focus involved, where the same influence is believed to so act, as an irritant, because it is not there so intense as to destroy the life of the parts.

Here may be introduced the statement that, while the agents producing a massive injury may sometimes at the margins of the injury act as irritants, and unless they spread as destructives as fast as, or faster than, the tissues can respond, sometimes do so, whether they are parasitic or not; yet are massive injuries not constant or necessary, for many of the irritants to act as such, and so for irritation to follow.

This truth is well seen in animals, perhaps better even than in plants; and although nowadays many inflammations which formerly were called idiopathic, because no irritant or extrinsic cause, locally acting, could be observed, are now believed to be due to microbic parasites in which an irritant influence inheres, although the irritant itself as yet is not in all cases positively separated, *e.g.* perhaps in tubercle and erysipelas; yet there remain others quite comparable and closely analogous to them, of which neither the parasitic microbe nor the irritant itself is known, the existence of which is not the less accepted without much question, as in syphilis and probably variola; and in all, the characters of the responses afford the evidence accepted as sufficient to show that irritants had acted, and that inflammation had followed.

Thus, more shortly put, it can be said an irritant can act as such with or without previous or present massive injury, and massive injuries may be produced by the agents of injury without necessarily acting as irritants; so that a distinction is sufficiently well marked between the actions of the agents of injury and injuries, and of

irritants, and these latter, even when not separately distinguishable, are confidently inferred in some true and accepted inflammations.

In animals, the employment of organic and inorganic irritant substances in experimental researches on inflammation has gone beyond any similar investigation in plants, with results which accord well with the above statements, and justify the view that in some respects the irritant substances and influences which are so constantly antecedents or concomitants of typical inflammation in higher animals are at present better known or accepted than are any equivalents thereof in plants. This statement stands, I think, although it is also true that, when the irritant inheres in a parasitic organism, the results shown in the responses are more obviously specific and fitly related to the irritants in plants than in animals, and especially so where the irritant is or inheres in a parasitic organism of a complex structure, of which the life-history has been well and successfully studied.

In animals, some such highly developed parasites are also fairly well known and have been studied ; but even in them the responses which follow show less of a specific structure in a fit relation to the irritant than do galls in plants, and are commonly but little more than a mere capsular fibrosis or a patch of scar-tissue, yet are always adequate for the purposes of the parasite, and are in some degree damaging as regards the host, although economical of disturbance to it. On the whole, there can therefore be little hesitation in concluding that the student of inflammation in man has something important to learn from the phyto-pathologist in regard to the irritant, and also has quite as much to teach ; and it seems not less certain that the student of general pathology should consider both plants and animals.

§ 19. (4) *The irritation*, or direct effect of the irritant in action, is in animals, as in plants, but a confident inference, and so only of hypothetical value; yet is it so strongly supported by facts as to justify a claim for its consideration as a working hypothesis.

Certainly it, like the irritant, may claim to be a constant attendant on typical inflammation. With various conceptions as to its exact significance, nearly all pathological writers employ the term, and are influenced by the idea, in treating of typical inflammation; although both the word and the idea are also involved in other disturbances of living tissue and tissue elements, and often are not so exclusively thought of as connected with inflammatory responses as I have endeavoured to show is here legitimate, or at least expedient. However, its reality, at least as a necessary constant antecedent and concomitant of typical inflammation, is denied by some pathologists.

Thus Samuel (*Entzündungsprocess*, 1873) says, "There is no irritant, no inflammatory irritation; the primary histological changes in inflammation are not active and histogenetic; they are passive in nature." But many critics of the idea oppose rather Virchow's conception of it than the thing itself. In all cases of irritation in plants and animals, whether related to true inflammation or not, it must be held to signify some disturbance of the substance of a living tissue or tissue element, short of arrest, or of a destruction of the life of the part; and it is followed necessarily by some vital responses, which are in all cases characteristic in some degree of, and due to, the evolved reparative attributes of such tissue or tissue elements; and should then be, although too often it is not so, recognised as also somewhat modified by the said disturbance or perturbation, and then as also characteristic of such perturbation or disturbance.

When, as often occurs, the irritation or disturbance is relatively very slight, and the response then is mainly, often indistinguishably, like that of the evolved reparative regenerative functions of the tissue or tissue elements, it is apt to be confused with a normal stimulation, with which it is or may be then admixed, as in many physiological experiments on muscle, nerve, etc., and after operations.

Thus may be explained, I think, the fact that zoo-pathologists consider the responses to irritation, although always really in some degree specific to it and to the irritant, as commonly related chiefly, if not solely, to the intrinsic reparative faculties of the responding tissue or tissue elements, although both intrinsic and extrinsic factors must co-operate.

It is much to be wished that the word stimulation should be thought of as meaning only that cryptic change of a tissue or tissue element which calls forth and may increase its normal response, without any admixture of the perturbation or disturbance spoken of above as irritation; but as in nature the irritation is always and necessarily accompanied by an active exercise of the said normal faculties, however modified, the ideas and the word used to indicate them have become often somewhat mixed and even confused. As Burdon-Sanderson has said, the irritation which sets up inflammation should be called "injurious irritation," and I adopt this expression. I will endeavour to keep the ideas distinct here, although in nature, in animals as in plants, it is scarcely possible to meet with concrete examples of irritation, without some coexisting stimulation, admixed, and certainly intrinsic responses always concur.

§ 19*a*. In animals as in plants irritation is here thought of as a cryptic change of the living cell-substance or of that of the cell-derivatives or complexes, and so it is not

amenable to direct observation. Speculation as to the nature of irritation is very strictly limited, and at present but little profitable; and as its manifestations in the responses must be the best, almost the sole, bases for any such speculations, this is not a suitable place in which to speak of any possible ones.

It is, however, here legitimate to say that in animals as in plants, and in typical inflammation, some irritant in action, and thus some "injurious irritation," are constant and necessary antecedents and concomitants in inflammation, as they are also in gall-growth; and this is not now very seriously disputed, I think, as regards higher animals. This statement does not necessarily imply that in animals or in plants all irritant actions result in responses which have as yet been generally called inflammation or its equivalent, because, in some common and even legitimate uses of the words irritant and irritations, some of the responses are not usually regarded either as inflammations or as their equivalents, in animals or in plants. See muscular movements, pains, or secretory phenomena in animals; and some comparable though less striking phenomena in plants, many of which, however, approach more nearly to the responses I would refer to stimulation, in the limited sense of the term. Hence, although in higher animals it can, I think, be said that without "injurious irritation" there is no inflammation, it cannot be said with equal certainty that with irritation of any kind or degree there is always some inflammation. This may be so, but it cannot here as yet be affirmed in respect of animals.

The same may be said of plants, only for them the words "response to irritation" must at present be used instead of inflammation, and the question at issue must not be assumed, strongly as I am inclined to hold that such

responses to "injurious irritation" as are seen in gall-growth are the equivalents of a true and typical inflammation in animals. I come, then, to the hesitating admission that at present only some irritations are accepted as causes of typical inflammation in animals, or of the equivalents thereof in plants, if these be granted as existing in them: for in each kingdom there are responses to stimulations which are often difficult to separate clearly from those to irritations, if slight.

This is a tenable position, and I think a sound one, because it is consistent with the known facts, with the specific relations of fitness seen between the responses and the irritations in many of the cases, as I have already stated, in plants; and, though less obviously so, also in animals. Also, it is consistent with the diversity seen in the irritants, and in the consequences their actions evoke in living organisms, and also in the irritations assumed as necessarily intervening between the irritant actions and the responses thereto, which diversities may rightly be regarded as specifically related to both cause and consequent.

So regarded, it is somewhat difficult to discuss the "injurious irritation" by itself; for it is not amenable to observation, and it is only clearly presentable even in thought in its necessary connections with the irritant cause, and with the responses it evokes. So far as is possible, however, these should be associated simultaneously. Although it is needful here to exclude, as far as may be possible, dealing with the responses which manifest the "injurious irritation" which leads to inflammation, it is convenient now to consider for a moment what it is that is irritated and responds in any true inflammation.

In higher animals, not less than in plants, this in the last analysis must be the living cell or the living cell-

derivative, the elementary organism. It is now, I think, universally agreed among biologists that living cell-substance is irritable, that is, that in response to impulses from without it exhibits changes of form, position, composition and structure; is sensitive, and mobile; also that its most constant and characteristic attribute is proliferation, and that it reproduces its kind under suitable nutritive conditions. Here the state of a possible irritation is implied in the existence of the faculty of irritability, and it is a normal one for the living cell in all organisms, plant or animal. The state of "injurious irritation," as related to the abnormal responses called inflammation in higher animals, is to be thought of as an abnormal one; and this is so in either kingdom of nature. It is always such as, while it leaves the cell irritable in some degree and mode, injuriously modifies its manifestations, as the responses show; yet is it, alike in animals and in plants, itself cryptic, although it is a necessity of thought, while so cryptic as not to be open to observation directly.

§ 20. (5) *The responses to injurious irritation* in animals, seen in typical inflammation, are the characteristic manifestations of it, and its consequences. They have, notwithstanding some fairly marked differences, the same ultimate foundations as have the responses to "injurious irritation," seen in plants, in that they rest upon the normal irritability of the living cell-substance or cell-complexes, as modified in and by the "injurious irritation" by the action of the irritant, are not annulled by it, but are directed or rather misdirected by it; and so they exhibit etiological as well as consequential relations.

In higher animals, in typical inflammation, the complexity of their structure and mechanism, and the functional and other mutual interdependences of their parts, involve an equivalent complexity of the responses to "injurious

irritations," as compared with those in lower and less complex animal organisms; and still more so as compared with plants, in which, even in the more complex ones, the cells and tissues of which are so much less immediately inter-dependent, that they show for each cell a greater amount of autonomy.

This fact may help to explain how it is that in the responses to "injurious irritation," as seen in a typical inflammation, cell-proliferation is so much less prominent or obvious a feature than are the vascular, nervous and other vital responses; which, however, are never in a true inflammation quite normal, or the sole ones, and never are unmixed with some perturbed cell-proliferations. Herein, however, we find that the strongly marked differences in the characters of the responses to "injurious irritation" exhibited in a typical inflammation, and in the responses to a similar irritation seen in the lowest animals, and even in the highest plants, are largely, though not solely, due to the divergent intrinsic attributes or reparative faculties of the responding things.

It should, perhaps, here be more explicitly stated that the vascular and nervous responses and all their connected phenomena, so usually accepted as characteristic of typical inflammation, are in some ways and degrees always abnormal and damaging to the responding organism, always involve some regressive changes in the focus, and thus have led to the general adoption of a fifth sign, impaired function, as an addition to the classical four signs—heat, redness, pain and swelling.

That some cell-proliferation is always present, and is then more or less in disorder as regards the organism, and often in a local excess in the typical inflammation of higher animals, although it may be then in a due order and proportion as regards the irritant by which it is determined

and misdirected, is, I hold, demonstrably certain; but this view is not the one generally taught; rather, the commonly accepted teaching still is, that the vascular and other such responses are constant and characteristic of the inflammation, that the cell-proliferations or accumulations are of later or secondary import, may even be absent; and the direction or misdirection of the responses by the irritant is not the generally received doctrine for typical inflammation; which takes, I think, too little account of the species or varieties of inflammation, and is concerned mostly with some demanded essentials of the whole process for all typical inflammations (see Cohnheim).

It is, however, now very generally ccepted that in many of the lower animals cell-proliferation in disorder as regards the responding organism, and often in some local excess, is a more constant and obvious characteristic of the inflammatory responses to "injurious irritation," and may perhaps then present us with the true equivalents of a typical inflammation, than it is in the higher ones; and I do not now hesitate to say, that it is the most constant known response to "injurious irritation," if we consider all animals as subject to that disease-process.

As cell-proliferation has already been shown to be the most constant manifestation in the responses to irritation in plants, it comes out thus as a constant in all organisms.

In animals as a whole it is less certainly shown that proliferative or other such responses are directed or misdirected by the irritant actions and are specific thereto than it has been in plants; yet is the evidence for this view sufficient to show that in animals also the effects measure and are measured by their causes, and that the responses in them are always damaging and regressive, and so they explain the fifth sign in inflammation, and

this in a strict relation to the "injurious irritation" and its cause, the irritant.

It may be, and indeed still is, disputed, whether the term inflammation can now legitimately be used to signify all those responses to "injurious irritation" in lower animals and in plants which are characterised by a misdirected specific local excess and disorder, in regard to the affected organism, so as to include the cell-proliferations or other responses seen in them, and thus to make them all in a sense the equivalents of a typical inflammation; but, of the close and real analogies between all the various responses to "injurious irritation" seen in higher and in lower animals and in plants, scarcely a doubt can exist—at least, none at all does in my mind. If this view be granted, the break between the characteristics of the various responses to "injurious irritations" seen in higher and lower animals is not very difficult to bridge over, and their continuous connection with plants cannot well be disputed. In typical inflammations, as seen only in the higher animals, their most obvious manifestations, whether vascular, nervous, or secretory and nutritive, are not less in disorder, and usually in excess as regards the organism affected, than are the proliferative ones when they are observed; and usually the former tend to obscure the latter, at any rate much more so than is the case in the lower animals and in plants.

In typical inflammation, therefore, it is much less easy than it is in plants, to demonstrate the direction or misdirection of the responses set up by the irritant through and by the "injurious irritation," and to show that the phenomena manifested, though disorderly in regard to the responding organism, and therefore damaging to it, are orderly and fitly adapted to the irritant, and directed or misdirected by it. Yet is this truth to be discerned in

these processes also, if studied in all animal organisms; and it has been found to be convenient and even necessary to do so on many grounds; and in this way it results that in all essentials such relations of fitness to the irritant are discoverable even in many typical inflammations.

§ 21. (6) *The responses to massive injuries without irritation —that is, simple repair.*—In speaking above of the responses to "injurious irritation," I have intentionally avoided much reference to the massive injuries often attending them, because they are not constant or necessary, although they are frequently present as co-operative factors, or sometimes as conditions precedent. The irritant in action, the irritation, and the characteristic responses thereto are separated thus rightly from the responses to a massive injury without irritation, in thought and in fact. In animals this separation is in some respects as well, or perhaps even better, seen than in plants.

In both kingdoms of nature, we must postulate as necessary for the persistence of living organisms, the possession by them of evolved normal reparative faculties, by which they deal successfully with non-fatal casual massive injuries; and in both kingdoms these faculties must rest upon the normal nutritive irritability of the cell, thought of as an elementary organism supplied with growth-materials or placed in a suitable nutritive environment. In the higher animals, which when "injuriously irritated" suffer inflammation, the responses to a simple massive injury are essentially and constantly efficient cell-proliferations and regenerations, with only so much of vascular and other equivalent responses concurring as may help the reparative efforts. This is a simple repair of injury. The phenomena, however, still rest fundamentally on the same original basis as do those which

manifest "injurious irritation," that is, upon the life of the cell or tissue elements.

The conditions necessary for such a repair to take place are, the injury, the living cells nearest not irritated but supplied with materials of growth, and an environment fairly normal for the organism, so that its cells and cell-complexes are free to feed, grow and functionate. Under these conditions, we find that living cells proliferate and develop, that is, regenerate, in accordance with their faculties in this respect, without, or with but little or no hindrance, so as to benefit the injured organism or part, which directs the responses, both cell-proliferative and circulatory, without disorder or excess or appreciable damage to itself; and in all this the contrast is obvious between a repair proper and the responses to "injurious irritation"; and it is the same in all animals and in plants.

In the higher animals, in such a repair process, it is true that the greater velocity of the vascular responses may make them more obvious, at least at first, than the cell-proliferations, just as in the responses to "injurious irritation," also, they appear to dominate and are more striking; but such vascular responses to "injurious irritation," like the cell-proliferations present, are then in disorder and in some excess, and so do damage to the organism; while the vascular changes attending a pure repair of a simple injury are well co-ordinated with the cell-proliferations, and are in fact to all appearance efficiently directed by the organism or its part, the purposes of which they serve; so that the distinction again is obvious, in the process and in the result, between repair and inflammation, for in the former the responses are fitly related to the responding organism.

In nature, it is seldom that concrete examples are met

with of a pure repair in a highly complex organism; so that in the vertebrata they are seldom seen quite unmixed with some "injurious irritation," or at least with some hindrances to pure repair which are apparently of intrinsic origin and due to the complexity of the structure of the injured organism. Yet are these relatively so trivial, when compared with any true "injurious irritations" derived *ab extra*, that the general theory of repair is not disturbed by this admission.

But better examples of pure repair are met with in some of the lower animals, which, in repair as well as in the responses to "injurious irritation," zoo-pathologists have been driven to include in the investigation. In animals, both higher and lower, as in plants, the product of the process of repair is, as I have said, distinguishable from that of the responses to "injurious irritation," in that it exhibits in the results adaptations and relations of fitness to the injured organism or part, is in quantity approximately proportionate to the injury, and by it some fairly effective compromise is brought about, of permanent service to the organism; so that its quality is thus indicated.

In animals, more especially, there is some reason to think, in those higher forms in which typical inflammation is met with, such repair, though not more constant, is more rapid than in plants; and this is probably due in some part to their possession of specialised structures and mechanisms for circulation, as well as to the existence in them of certain tissues, *e.g.* the vascular connective specially, endowed with high reparative cell-proliferative faculties for tissue regeneration; and there is seen also in many of their epi- and endothelial tissues a similar provision, which perhaps compensates in them for some relative deficiencies, in these respects, of similar attributes

in some other animal tissues, more specially endowed in other ways, as we see in ganglion cells.

Repair, at least in the higher animals, if it be more rapid than in plants, is more limited in its results; seeing that, although it very rapidly heals over or unites wounds and even regenerates tissues, at least of some kinds, though not all, it much less often regenerates organs or members in them. For this response we must go to the lower animals to find comparable faculties for such regenerations, which in them, as in plants, are often complete, and may reproduce even a whole organism under suitable conditions of the organism and of its environment.

Responses to a casual injury without "injurious irritation" intervening are then exertions of evolved faculties or functions, and vary with the intrinsic reparative faculties of the injured organism or of its part. For their due manifestations, all that is required is to defend the injured organism or part from extrinsic interferences with the exertion of such a normal function, and to secure normal conditions of nutrition; and this is so for all animals and all plants, and is repair. The process is, in essentials, the same for both kingdoms of nature, notwithstanding some less important differences, and the language in common use admits the oneness of the process, of its results, and of its conditions.

Although this oneness of repair, as to its essentials in the process and in its result for all animals and all plants, is, I think, universally accepted; and although this response to casual massive injury should be accepted as resting upon the self-same vital attributes or faculties of the cell as do the responses to "injurious irritation"; yet is it not quite generally accepted among pathologists that the responses to "injurious irritation" belong to the same category in all organisms; and these

latter are called inflammation in the higher animals—and indeed nowadays sometimes, though not often, also in the lower, although not even then in its typical form; and when responses to "injurious irritation" are met with in plants they are by most pathologists not so named, are indeed commonly left unclassed. For this distinction I see no good reason, and I have seen none stated which will bear a critical examination.

The use of the term response in respect of a pure repair process is convenient, and difficult to do without; but it does not mean quite the same thing as it does when it is used in regard to irritant actions, closely related as are the two ideas. In a response to a simple injury, it is here said that the organism or its part, normally functionating, though under an unusual condition, directs such a response in lines normal to it; and to this end it does not demand and must not have any new or interfering extrinsic irritant influence acting so as to determine the response or direct or misdirect it, but it uses to this end only its own intrinsic evolved reparative powers or faculties.

Leaving for the moment as an open question, whether or no, in normal nutrition, growth and repair of waste, a normal growth-enzyme is required as a stimulant to initiate a movement, it is held here that in a pure repair of a simple casual injury the defect or injury itself does not necessarily introduce any such new extrinsic influence, nor any directing or initiating force, such as an "injurious irritant" does, or at anyrate is here assumed to do, although the injury may, and probably does, act by changing the pressures and the competitions for growth-material, and so may set free growth and development of the nearer uninjured cells and cell-derivatives, by its collateral influences.

In all animals, as in plants, repair of a simple casual injury stands in a very important and close relation to the responses to "injurious irritation"; but it is one of antagonism in both kingdoms of nature; and although the prime mover is the same in both, that is, the evolved reparative faculty, the results of the two processes are not only different but opposed; and this is so both in responses to "injurious irritation" called typical inflammation, and in those to which that name is not yet generally granted, but are, as I think, its equivalents. It seems evident, then, that light might be thrown upon a question much needing it, were plants and animals considered both together, seeing that they are all living organisms in which phenomena constantly occur having much in common.

§ 22. (7) *The Etiology, extrinsic and intrinsic, of the damaging responses to "injurious irritation," and of the reparative ones to a simple injury.*—As here the word is used, etiology includes the consideration of, not merely the constant and necessary antecedents, concomitants, or causes, but their relations to the consequents or effects, such as may indicate the real and necessary equivalences of causes and effects. Hence, for the completeness of the idea of the cause, it is required to include a consideration of both the extrinsic and intrinsic factors thereof; and for a satisfactory conception of the consequence as effect thereof, it is needful to appreciate its relation of fitness and equality to the cause. The constant antecedents and concomitants of the responses to "injurious irritation" and to simple injury, *i.e.* of inflammation and of repair, both the extrinsic and intrinsic factors, have already been given, and have been shown to be the irritant in action upon an irritable cell in the former, and a solution of continuity or a loss of material in the latter; so that it is not now

needful to repeat examples of the agents of injury, or of "injurious irritation," or of wound-production; and it is only requisite to deal here, in regard to animals, with the relations of fitness shown by the consequences or responses to their causes in inflammation and in repair, in such a manner as may make such relations intelligible in both orders of response, and may exhibit their distinctions as well as their resemblances.

As I have already anticipated somewhat in speaking of repair, and spoken of its relations of fitness to the injured organism, and of equality in quantity to the injury, and of quality to the part responding, and noted that in this process an essential oneness is generally accepted for it in all organisms, plants and animals, it will not be needful to say more on this point here. But, in respect to typical inflammation, it must be observed that the responses to "injurious irritation" have not yet been here shown to exhibit evidences of relations of fitness to the irritant in higher animals at all equal to those which have been shown in plant galls, nor even as in the less typical inflammations or their equivalents, as they are seen in lower animals. In fact, the adaptations and relations of fitness shown by the responses to the irritant, even when it is also a parasite, are less strikingly obvious in most animals than they are in plants; although they are, I think, more so in the lower than in the higher animals, and are to be found, if carefully sought for, in all animals, higher or lower, whatever be the irritant, *i.e.* parasitic or not, and they are always manifested in cell-proliferations.

Briefly I recall here the relations of fitness traceable in the suppurative inflammations, especially those which, like variola, run typical periodic courses, between the responses and the microbic irritants which are believed to be their causes. However, when the "injurious irritant" is non-

parasitic, such relations are more obscure, yet even then not quite wanting; and as, especially in the higher animals, the non-parasitic irritants have been more studied and are possibly more frequent and effective than in plants, the responses to "injurious irritation" in them which have received the greatest share of attention are just those which exhibit the least evidence of relations of fitness to the irritant. This may help to explain the fact that, in typical inflammation in the higher animals, relations of fitness or adaptations to the irritant shown in the responses are either ignored or denied by most animal pathologists, if not by all; and relations of fitness have even been very widely asserted to exist, between typical inflammation, with its responses and products, and the responding suffering organism.

The greater complexity of structure and the more immediate interdependence of the parts of these higher animals also complicate very much the problem before the investigator; so that it is or has been, in the responses to an almost pure trauma, often scarcely possible to separate with certainty extrinsic parasitic irritating agencies from non-parasitic, or even from other parasitic ones, of some kind, perhaps possibly derived from the injured organism and intrinsic to it, although extrinsic to and pathogenic to the part, that the examination has been chiefly influenced.

In this way much of the experimental investigation of typical inflammation, prior to the full development of bacteriology, was carried on in animals such as frogs, etc., without any adequate separation between parasitic and non-parasitic, extrinsic and intrinsic irritants, and the processes set up thus, by causes not analysed, were studied largely, almost exclusively, in regard to their obvious characters as indications of inflammation as a whole, and

not in any special relation to the particular species of the response, or to the particular irritant by which it was set up. So studied, the object kept in view was to find the constant amid the variable, the demanded essential for all typical inflammations; and however important this object may be, and is, as a result of this method, under conditions which did not admit of accuracy, the effect has been some relative neglect of attention to the etiology of the specific differences of the inflammations or responses in relation to their particular irritants, *i.e.* to the extrinsic agents of "injurious irritation," and a relative preponderance of attention was given to the intrinsic factors; and thus etiology proper has been relatively neglected, at least in the sense of the term as here used. To all appearance, some later effects of these earlier modes of investigation are still with us, although the bacteriologists are doing much and good service in correcting some of them.

From these, and perhaps other such reasons, it has resulted that non-parasitic irritants as causes of inflammation in higher animals have even recently been given a very large, I think too large, a share of importance, the kinds of response they evoke have not been duly distinguished from those evoked by parasitic irritants, and the relations of fitness between causes and consequences have not been sought with sufficient attention to this point, at least such as could separate the kinds of responses; and thus etiology has not had its due weight.

Nevertheless, the progress of bacteriology has shown in the specific inflammations, even in the highest animals, an increasing tendency to exhibit some relations of fitness between the products of inflammation and their particular irritants, though far less clearly than we see in plant galls; and as the typical inflammations are more and more found

to be set up by parasitic irritants, they are almost daily increasing in importance, in proportion to the non-parasitic inflammations, and so they illustrate the nature of the process as a whole. As, however, these parasitic irritants are all, or the most important of them, colonies of micro-organisms, in which the individual interests of each parasite are less clearly seen in their life-histories than in gall-producers, one would scarcely expect to find in the responses they evoke relations of fitness and adaptations as clearly shown as we find them in plant galls, the producers of which are often higher parasitic organisms, with better known life-histories and more obvious interests; so that in them the etiology is more clearly manifested, and its relations to the responses are more distinctly exhibited.

Etiology being then so thought of, it would help much to consider, as I think we may now for a moment do, all animals and all plants together, in regard to the responses to "injurious irritation" exhibited by both of them; for even though it is true that the relations of fitness to the irritant spoken of are not so well seen in animals as in plant galls, yet are some traces of it seen in all; and the consideration of the whole group together may afford help to, and give more light upon, each of the parts of it, when compared, and this I now contend for.

§ 23. (8) *The responding mechanism, and the characters of each order of response.*—In animals not less than in plants the fundamental basis of the responding mechanism is the cell, the elementary organism; and this is so for each order of response, the efficient or truly reparative, and the inefficient or damaging one; and this truth is demonstrable in them as clearly as in plants, if all animals be taken into the field of view. It is, however, required to be recognised that, especially in the higher animals, in the

ratio of their complexity, cell-complexes and tissues so enter into the responding mechanism as to modify very much the dominant or obvious characters of the responses of either order, yet without impairing the essential distinctions between the two orders, which thus always remain in the one case beneficent to the organism, or efficient, and in the other damaging to it, or inefficient.

Thus, the same living irritable cell-substance which in normal nutrition repairs waste, or after a casual wound, if not prevented or perturbed, repairs the injury and restores the loss by cell-proliferation and development; when prevented from so acting, or when perturbed, as in "injurious irritation," is itself a cause of damage; and the responding mechanism or *automatic reparator* is then by its own perturbed action the very means by which damage is done, even in a typical inflammation, not less than in the allied or equivalent responses to "injurious irritation" seen in the lowest animals and plants; and this is not less true, and demonstrable, when the more obvious responses are from cell-complexes and tissues, as in hyperæmia, than when they are from cells not so associated, as in non-vascular organisms or tissues.

In unicellular animals, as in multicellulars, the same general truth stands, with some minor qualifications, though not such as contradict the broad statement that the same living elementary organism which can itself repair a simple casual injury by an efficient process of proliferation of its own structural units, also can, when modified by "injurious irritation," not only antagonise repair, but also itself does damage by an inefficient exertion of the same powers, and by the misdirected proliferations of its structural units, then forced to act in correspondence with, that is, to show relations of fitness to, the irritant, and no longer serviceable to the organism as a whole. It

must, however, be granted that in this field of work much has yet to be done, and the responses to a casual simple injury in unicellulars, and still more those to "injurious irritation" in unicellular animals, are by no means satisfactorily known as yet. In multicellular animals, however, as in plants, research in this direction has been much more extended and, I think, successful.

It has been said truly that in both kingdoms of nature pure repair is the normal response to a simple injury, and in both it is the characteristic of this order of response to correspond in its results with the interests of the organism, or of the part, and to do so by a process in which cell-proliferation, duly co-ordinated, is a constant character, so that the response is efficient. In inflammation, or in a response to a true "injurious irritation," by whatever name it is known, it is a characteristic of this order of response to be inefficient, that is, to correspond in its results with the irritant, and not with the organism or part of it responding; but rather to damage it, and to do so by a process in which the cell-proliferation is in disorder and often in excess in relation to the organism, and not duly co-ordinated with the local supply of growth-materials; and this excess and disorder is a constant character, although it may be usually in the higher animals obscured in the vascular responses.

Although far less clearly than in gall-growth in plants, the correspondence in the results of such inflammatory responses with the interests of the irritant can be often ascertained when sought for with due care, yet is the relation of fitness of these responses to the irritant in higher animals usually either ignored or denied by animal pathologists, and often the converse of it is confidently asserted.

On this point it must be granted that a well-marked

difference, certainly of view, and, though less clearly, also to some extent of fact, exists between the responses to "injurious irritation," as seen in gall-growth, and those which we call typical inflammation in the higher animals. The evidences of the relations of fitness with the irritant in gall-growth in plants are so obvious as to force themselves upon the attention; while in typical inflammation in higher animals, and even perhaps in its equivalents in lower animals, they have to be sought for with great care, or they elude observation. While, therefore, in inflammation in animals it is granted that the evidence is less obvious of the directing influence exerted by the irritant in action upon the responding mechanism of the organism, and coercing it to respond for the benefit of the irritant, than is the case in the responses of an apparently similar order in plants, there is in the inflammations, as seen in animals, ample and obvious evidence that the responses here dealt with are not beneficent to the responding organim or its part—are, indeed, always more or less damaging to it, and so one may say with much confidence are not directed by it, while they never damage the parasitic irritant, but seem always to serve its interests. All animal pathologists, I think, grant that in inflammation damage is done during its presence as a process, and although much divergence of view obtains as to the significance and importance of the damage, its constancy is, I think, universally admitted. The inference should be, I hold, that this constancy of damage in the process is due to the persisting directing or misdirecting influence of the irritant in action upon the responding mechanism in animals, and to the concurrently impaired directing influence of the responding organism which suffers the damage; that is, therefore, to the misdirection effected by the irritant on the intrinsic reparative faculties.

Therefore, the constant damage done during an inflammation and by it in animals, though in it such relations of fitness as are shown in plant galls between the responses and the irritant are more difficult or often impossible to trace, is evidence enough that the irritant actions, when present, impede or arrest or misdirect and antagonise the beneficent responses which, in the absence of such irritant actions, are constant and efficient in all non-fatal injuries in animals not less than in plants.

Even, therefore, when such relations of fitness to the irritant are apparently absent from the responses to it, the damage so constantly seen present sufficiently shows the influence of the irritant as an essential factor in the production of this constant, or, as one may say, as the director of the events in respect of damage. Such damage is quite as constant in inflammations in animals as in the inefficient responses to irritation as seen in plants; it is, especially in typical inflammation, perhaps even more severe, and in both kingdoms of nature it is so constantly related to "injurious irritation" that it may confidently be stated to be measured thereby.

How this damage during an inflammation is done is not always easy to demonstrate in many cases; but that some of it, and that to which the word damage in strictness might with advantage be limited, is due to the disorder and local excess of the proliferative and other responses evoked by the "injurious irritation"—in other words, that it is due to the inefficient and misdirected working of the *automatic reparator*—can scarcely be questioned; and this is so, whether the responding thing be a cell or a part of one, a single cell, a cell-complex, or a tissue closely related to other tissues, and to the whole organism, such as vessels and nerves and their dependent tissues and organs.

Any, or each, or all of these responses may and do, often in virtue of the local proliferative disorder or excess in them, often produce a local necrosis, which, whatever of benefit it may confer upon the irritant, as in some cases it seems to do, is always a damage to the responding organism, even although some compensations for it may possibly follow.

Such necrosis, although indirectly it may be due to the actions of the irritant, is not ever the immediate and direct effect thereof, for the irritant must not kill. When an injurious agent directly acts so as to produce a necrosis, it is not then and there as such an irritant, whatever may occur at the periphery of the necrosed focus, where indeed, as already shown, "injurious irritation" is almost a constant sequence. I exclude here, for clearness of mental presentation, the cases in which the agent of injury had directly caused necrosis, and I take into consideration here and now only those cases of inflammation, or responses to "injurious irritation," in which the irritant actions were from the beginning solely such as produce "injurious irritation" and its consequences. Then, all the subsequent necroses, if any come, must be thought of as doing indirectly the damage in the technical and limited sense of the word, as it is above used; because the tissues and tissue elements so necrosed had all been previously proliferated and modified injuriously by the irritation, and in the proliferative and other responses thereto; and thus these are not merely direct or passive effects of "injurious irritant actions" or of injurious agents, but are indirect consequences of "injurious irritations," and present certain characteristic vital phenomena.

However, especially in a very typical form of inflammation, *e.g.* a suppuration from the "injurious irritation" of some pyogenic bacteria, without any known initial breach

of continuity or any necrosis at first, some necrosis occurs later, constantly ; and then it must, I think, be held to be a consequence, at least in some part, of both the indirect and the direct actions of the irritant upon the tissues and tissue elements of the focus as they are changed, in some order and degree not very well known. Such a necrosis may be due in some measure to the cumulative, complex and diverse effects of the numerous irritants acting, and in some measure to changes in their modes of action dependent on their being then, or some of them in a later stage of development, such as demand the change ; but always in greater part due to the fact that the tissues and tissue elements in the said focus had been already irritated, that is, injuriously proliferated and modified by the irritant, and adapted by it to its own purposes and ends ; among which a necrosis of the tissues of the host at the part is one, and it is often an essential one for the dispersion of the germs for the production of other suppurations of a like kind. Thus, I would suggest an explanation of the known fact that all suppurations tend, though not all succeed, to escape at some surface, internal or external, and do this by means of a necrosis commencing approximately at the centre and spreading outwards.

Such a view harmonises very well with what is known of gall-growths in plants, and it enables one to comprehend, if but dimly, how it is that the damage done in a typical inflammation may be, in part at least, directly due to initial injurious actions of the irritants upon the cells and tissues of the focus, and thus not all and solely to the misdirection by the irritant of the responses in a tissue ; while yet it must be conceded that the damage done in and by, or during, an inflammation cannot be correctly apportioned between the inefficiencies of the misdirected *automatic reparator* and the repetitions of the

directly injurious actions of the irritant, varied, it seems probable, in kind and degree at different stages of the process, producing injuries, sometimes even fatal ones, upon the often previously irritated tissues.

So, I think, may be explained how it is that pyogenic bacteria may first determine an emigration of leucocytes in excess, and other similar or allied phenomena of tissues and their elements; and later on may perhaps kill, and apparently live upon them, and may thus enable their progeny to disperse and the parasitic species to survive; so that the steps in the whole process, the irritative and the destructive, can be thought of as directed by the irritant, and both phases of it as presenting some relations of fitness to it, even if less clearly, perhaps, than are seen in plant galls.

Some galls due to colonies of very minute organisms of widely diverse origins show a somewhat similar series of phases, in which the irritant determines an abnormal hyperplasia in the beginning of the process, and a necrosis at or near to its end; and both phases then subserve the purposes and needs of the irritant, and adversely influence the host plant, so that damage to it is a constant, while fitness in relation to the irritant, though less strikingly marked than in some other galls, can still be found if carefully sought for.

So therefore, in animals as in plants, responses to true "injurious irritations" present us with damage to the responding organism as a constant character, whether such responses be called inflammation or not, and however such damage may be done: the responses benefit the irritant which, I say, directs them. Thus, in this order of inefficient response in both kingdoms of nature, such responses show, though with different degrees of clearness, some relations of fitness to the irritant, but not to the

organism, which they always damage. And yet in both kingdoms of nature, in the reparative responses to simple casual massive injury, a relation of fitness to the organism is always clearly visible ; and it is approximately equal to the injury. So also in both kingdoms of nature the elementary organism, the cell, is the basis of, or the responding thing for both orders of response, the efficient and the inefficient ; and the most constant manifestation of its action is proliferation of structural units of cells or of cells ; nor is this truth weakened by the fact that cell-complexes also respond, in each order.

§ 24 (9) *Recovery after the responses to "injurious irritation," i.e. inflammation, in animals, compared with a Repair of simple injuries.*—What is known as *Recovery* after inflammation in animals is so frequent that it is usually accepted as the rule, and has at times even been spoken of as a character by which certain inefficient responses to disturbances, not accepted by most pathologists as inflammation, and not so terminating, may be distinguished ; for example, some so-called tumours or new growths, even when they are admittedly determined, at least in part, by irritant actions. *Recovery*, however, after a true typical inflammation is not a constant in animals, any more than it is in plants after their responses to irritations ; and not only local death of some portions at least, if not of the whole of the focus involved, is so frequent in it as to be by some authorities deemed a constant ; but often also when, by the persistence and spread of the irritant actions, the responding process continues as long as does the life of the organism, recovery does not take place at all ; and we say the case is fatal, that is, to the responding organism, though not so to the irritant ; the inflammation has, in fact, persisted as the irritant action has, and for this reason there is no recovery after it.

I note here in passing that some, perhaps only a few, of the new growths suggestive of, and which may possibly be responses to, irritation, which are always and confidently called tumours, do also occasionally recover (*e.g.* sarcomata); so that this point on this ground cannot be used confidently as a distinction in diagnosis.

Recovery after inflammation in higher animals, or, as the phrase usually runs, from inflammation, has received a very large share of attention, chiefly, I think, in relation to the details of treatment of the malady, especially so in man; and the opinion has been held, perhaps justly so, that it is more frequent and complete in him than it is in plants; but as the existence of a real and true equivalent of the process called inflammation in plants is not generally accepted, it is difficult to make a due comparison in this respect.

On the whole, I must be content at present with the statement that recovery is more spoken of and considered in higher animals than in plants, and its manifestations are in them perhaps more striking, without as yet pronouncing a confident opinion upon the relative capacity of animals, as compared with plants, to recover after the damaging responses to "injurious irritation," or upon the modes by which such recovery does take place or is effected, its frequency or completeness, or the resemblances and the differences of its manifestations, in the two kingdoms of nature. But that it does occur in plants under certain conditions and in some degrees has been shown in the last section.

In one very important respect both plants and animals are alike—in that recovery demands as a condition precedent that the irritant actions, the "injurious irritations," shall relatively or absolutely have ceased, or so diminished as no longer to dominate or misdirect the responses.

Hence the correct expression is recovery after inflammation, not from it.

For the moment, I will disregard the question as to how or why the irritations often so cease or diminish, but hold fast here by the fact that, unless they do so and until they do, recovery does not begin. In another not less important respect, there is a like agreement in animals and plants, namely, that when the irritant actions cease to dominate the responses, then the evolved intrinsic reparative faculties of the organism, as represented by or contained in the cell, *i.e.* those by which it effects a repair of waste, replaces a loss, or heals a wound, become themselves dominant, having previously, *i.e.* during the whole period of the damaging responses to "injurious irritation," been modified and suspended, not lost: so that recovery in its essentials is but a return to repair under conditions somewhat different from those which obtain in a normal repair of waste or of a simple injury, yet not such as materially impair the essential oneness of the two differently named processes, and indeed under normal nutritive conditions such recovery is necessary and constant.

Recovery, therefore, is but deferred repair. Thus, in animals as in plants, recovery is but a return to, or at least towards, the process of normal repair and nutrition; and as this repair has been shown to be as constant and necessary in plants as in animals, even if less rapid, and exhibited in different ways, yet is it not less adequate for the maintenance of the organism; it results, therefore, that there is no sufficient reason apparent for expecting that animals should recover from inflammation more completely than plants do from such damaging responses to irritation as they suffer from, even if they do so, as has been said by some authorities, more rapidly, and in

different modes. In short, there is a general consensus of opinion that repair is essentially the same thing in plants and in animals, and if this be so, then recovery, or delayed repair, is also so, and like it is also necessary under proper nutritive conditions. There is also a similar consensus of opinion, that, given the cessation of dominance of the irritant actions, from whatever causes, and given also normal nutritive conditions of the tissues around, recovery is as constant and necessary as is repair after a simple injury, in both kingdoms of nature. *Recovery*, then, demands in animals as in plants an absolute or relative cessation of irritation in the focus, with the co-operation of the evolved intrinsic faculties and adequate nutritive conditions in the area around it; and then it is assured.

§ 24*a*. Now a word or two must be said as to how and why irritant actions and the responses due thereto sometimes cease or relatively diminish, so as no longer to dominate and direct or misdirect the responses, and sometimes do not, either in animals or in plants.

Where the agent of irritation is a parasite, it is well seen in plant galls, when such an agent is itself a complex organism of which the life-history is known, that such a cessation of irritant actions is much related to and dependent on its own stages of development; and the responses evoked vary then in quantity, intensity and kind therewith, yet always so that the responses evoked never fail to accord and correspond with the needs of the parasite at each such stage, never arrest appreciably, certainly never successfully conflict with them or cancel them; but as they began with, so they continue with and end in a due correspondence each with the other. The proofs of this general statement in plant galls are afforded in the study of the beginning and progress of the formation of a gall-

plasm (see Beyerinck[1]). Whether a wound be present or not, the responses begin with the "injurious irritation," and progress in an exact correspondence with it in all phases and stages, and measure it.

If the parasite rests, as in the pupa stage, so does the irritation which it determines, and the responses thereto; when the mature parasite escapes, the responses are such as had often in many ways helped thereto; even although such escape increases the risks for the host. Throughout the succession of changes in the focus of irritation, the host tissues, as has been said, always suffer some damage, if sometimes only a minimum; but always the necessities of the parasite have been duly provided for, without which, indeed, no parasite could be established as a species. In plant galls, then, the relative diminution of the irritation, the necessary condition precedent for the beginning of recovery, is initiated by the normal developmental phases of the irritant, and so it is in a sense autonomous or spontaneous; and the same statement is often true in inflammation in animals, when it is due to a parasitic irritation; although to say so is a sort of pathological heresy.

In animals, where the inflammation is of parasitic etiology this same broad truth must, I think, hold, whatever qualifications are or may be demanded in an inflammation due to non-parasitic irritation, which in them has been given a somewhat greater relative importance than in plants; though nowadays such importance of non-parasitic inflammation is less than was the case before Pasteur—indeed, much less than that given to the parasitic typical inflammations, especially if we take the gravity

[1] "Beobachtungen über die ersten Entwicklungsphasen einiger Cynipiden-gallen," von Dr M. W. Beyerinck (*Natuurk. Verh. der koninkl. Akademie, Deel*, 1882).

or intensity of the process into account, as we should do, as well as the type.

There are some cases, of which the so-called chronic inflammations afford fairly good examples, which, though due mostly to parasitic irritation, do not apparently tend spontaneously to cease; and these are here of interest to the argument, as illustrating the persistence at the same time and place of the irritant in action and of the responses evoked by it, and their connection with the multiplication in or near the focus of the parasitic irritant in action, without any obvious previous arrest or cessation of its actions, in a sort of pupa stage, or otherwise, and often without a complete separation and escape of the irritants as a colony or as spores.

Here there is no question of recovery, for its condition precedent, the cessation of the irritant actions, absolute or relative, either does not take place, or is more than compensated for by multiplications of the parasitic irritants for the reproduction and persistence of which *in situ* the host organism supplies the means and the favouring conditions. It is not doubted that individual parasitic microbes in the colony ripen and pass through their normal phases, and escape or die, or even may perhaps sometimes be killed; but the colony itself survives, and it is enabled by the help of the host to disperse its spores, to its own advantage, and renew or in some way extend the responses, *i.e.* the malady.

These cases in no way contradict the statements above given, which are founded upon the study of the responses to single parasites in plant galls, which, having developed, escape from the host when dispersal is all they need.

It must, however, be freely granted, that in animals the study of the responses to parasitic irritations and of typical inflammation, which in so large a proportion

of cases is of microbic etiology, affords much less clear evidence of the spontaneous cessation of irritant actions, as a normal outcome of the development of the parasite, than does the study of plant galls; and so it might be plausibly said that to adduce these cases as I have done as illustrations of an argument relating to the cessation of inflammation in animals is scarcely legitimate; but to such a criticism a sufficient reply, I think, will appear below.

Thus, if we direct our attention to the higher animals, and chiefly to man, the conception, which it may be granted was first suggested by the study of plant galls, finds very great support, and the alternative one very little. The general biological truth that all organisms, parasites not less than others, pass through some necessary phases in their life-cycles, multiply, and then disperse, so as to preserve the species, though the life of each member of it is limited, justifies us in concluding that the parasitic microbes causing, say, a suppuration, like the parasites which cause plant galls, pass also through some such phases, and that their actions as irritants vary in the different phases of their life-cycles; that these phases tend to end, and though at least some of the individual microbes die, the germs for future colonies must live and be dispersed, for this is the law of their being and persistence as established species of parasites.

Suppurative inflammations and many others, if considered in the light of this general view, offer us examples which seem better explained by it than by any other alternative I know of. Acute specific exanthemata, such as variola, the periods of which can be predicted, are fair instances of this; for it is scarcely possible to refer the actual cessation of the specific irritation to any other reason than to the maturity of the multiplied microbic irritants, and to their need for dispersal at or near a fixed period;

and it is consistent with this view to think of the febrile and earlier eruptive phenomena as responses to "injurious irritation" in an earlier and different stage of the life-history of the parasitic irritants; and the later phases as connected with a relative cyclical and normal cessation of such irritation, and a dispersal of the spores, when this is the greater need of the parasite. I would therefore refer the periodicity of the vast group of specific inflammations, often if not always associated with fever, similarly to the periodicity of the life-phases of their respective parasitic irritant causes—an opinion which must, I think, be greatly strengthened since the discovery of the parasitic etiology of various fevers, most if not all of which are associated with true inflammations. In every case of typical inflammation due to the "injurious irritation" of parasites, the varying yet constant and necessary phases of the life of such parasites must influence the characters and duration of the irritation, and must also be factors influencing its cessation, if and when the inflammation does cease, or recovery can begin.

Whether or no this is the chief or the sole factor in bringing about that cessation of irritation, absolute or relative, which must precede a recovery from such inflammations, I cannot here say positively; but this factor, I think, is certainly always in some degree operative, and cannot rightly be so much ignored as it has been.

What has been said above about chronic inflammations with persisting and multiplying parasitic irritants, almost excludes such responses from any true recovery as it is here thought of. The specific acute periodic inflammations do show such a process of recovery, and its relation to the normal cyclical changes in the irritant is shown in the periodicity. But many acute suppurative typical inflammations, *e.g.* abscesses, also show that, by the process

of inflammation, a provision in advance is made for the escape and dispersal of the mature microbic irritants, which is comparable with some of the changes seen in gall-growth and development—*e.g.* the pointing, the escape of pus, and the subsequent or consequent recovery; and it is a reasonable conclusion that the microbes in such escaping pus are mature and fit to disperse and multiply elsewhere, for it is known that the pus is infective.

True, we do not know much of the earlier or cyclical phases of the said pyogenic microbes, as these have not, I think, been investigated with sufficient success; but there are no good reasons known to me which justify an assumption that they differ from other living things, and do not pass through similar phases of evolution, or that their action as irritants is alike at all stages from the beginning of the suppuration to the bursting of the abscess. I therefore conclude that the earlier phases are unlike the later ones. Even now it can, I think, be said that, as in plant galls so in animals, in parasitic inflammation, in many cases at least, this factor is a real and an effective one in determining the diminution and cessation of irritation, and thus the spontaneous beginning of recovery.

Hence, not only is repair to be regarded as normal, but recovery, when it occurs, is also so in all such cases; it is then a natural and not solely an artificial event; it depends largely for its beginning on the life-history of the parasite, and not upon the phenomena of the responses evoked in the host organism.

A justification of my having used the parasitism of gall-growth as an illustration of this doctrine, is therefore that the suggestion arose from its study; that it exhibits the truth clearly; that it is one which applies to all parasites, and that so it applies to parasitism in animals also, as an

illustration of a truth common to both kingdoms of nature. Helped by the clue so given, it is not very difficult to trace the same necessary relations between the parasite and the host in the responses which animals present to us as we see in plants ; the same necessity must exist for a parasite to pass through its own phases of development, and ultimately to disperse, and to find or produce corresponding changes in the responses it evokes, and thus itself to determine for its own ends a relative cessation of irritant actions as a condition precedent for recovery of the host, in animals as in plants.

§ 24*b*. This conception of the beginning and the cause of the relative or absolute cessation of irritant actions as the condition precedent to recovery from or after inflammations, is almost diametrically opposed to the now dominant teaching, or at least the most widely prevalent one, which is the only alternative I need consider. The widely current teaching, put as fairly and as briefly as I can, says that inflammation is itself a somewhat salutary or reparative process, or a sort of struggle against the irritant or that in which it inheres by the organism or the part of it affected, in virtue of which the irritation is cancelled and the observed actual cessation of the irritant actions is not imputed to any normal phases in the life of the parasitic irritant, the effects of which are ignored, but rather to the exertions of the responding and damaged organism, which, it is taught, tend to expel the irritant or to cancel the irritations.

The teaching of this school does not deny, or even doubt, that during and by this process some damage is constantly done to the responding organism, or that recovery cannot begin until the irritant actions are in some way at least relatively, and in some considerable degree, reduced ; but not the less does it maintain that by, and

in virtue of, the responses themselves to the irritant actions, the irritation is cancelled or the irritant is expelled, and in support of this doctrine the phenomena of phagocytosis are much appealed to; they are made to serve as some of the chief grounds upon which it is maintained, and they are without doubt of some weight; yet are they not such as are adequate to resist the difficulties and even contradictions which this teaching has to surmount.

This doctrine is, I think, a survival in some of its main features of the ideas which dominated many surgeons before Hunter demonstrated that inflammation antagonised and during its existence prevented repair; and it requires the inadmissible assumption, that a process which does damage, and prevents repair, prepares for it by cancelling irritation, the cause of the process. Hence it was formerly taught, and, alas! also practised long after Hunter, that inflammation, especially the suppurative form of it, was to be encouraged, in order to bring about a recovery by a separation of the irritant. The doctrine in this form is now happily dead, but its spirit survives in a new form which is widely accepted. And it is now maintained, even by many of those who recognise the paramount importance of parasites in the etiology of typical inflammation, that the responses they evoke themselves bring about the cessation of the irritant actions, and so make a recovery possible. Also it is taught now that this is the purpose of such responses, although this is not proven, and it is, I hold, not possible to be so; for it says that the parasites which cause a typical inflammation, unlike all other parasites, determine in their own produced environment within their hosts, conditions destructive to themselves, although it is certainly known that in all such cases the said parasites flourish and multiply exceedingly; and finally, when they are dispersed are abundantly fertile and virulent, as is

seen in the pus from an abscess or from a variolous pustule.

Neither in animals nor in plants can I recall any single instance in which the responses to an established parasite are so adverse to it as to cancel its action or arrest its development, or even materially to hinder it; but rather, wherever such a parasite is established, there it flourishes, and the host helps it to grow, multiply and be dispersed; and were this not so, that parasite would not there be established.

§ 24*c*. I need not here dwell much on, but may briefly mention, some of the more obvious objections to this doctrine that inflammation is a reparative process, or in some way beneficent to the suffering organism.

Thus, (*a*) that during the whole of the *actual process* it constantly and continually does damage; (*b*) that this damage is great as the inflammation is intense; (*c*) that recovery, or true effective reparative changes, only then begins when the inflammation and irritation have ceased or are ceasing, from whatever cause; (*d*) that in the typical inflammation process, itself of parasitic origin, it is difficult, or to me so far impossible, to find any evidence that the process is itself salutary or reparative to the affected organism; or (*e*) that it itself determines a diminution or cessation of irritation, or by its own exertion ever brings about its own termination.

Although inflammation is a terminable or a temporary process often which begins when irritant actions do, progresses with them, and ends when they cease; yet, as it is throughout a damaging or destructive one, so long as it endures, it cannot itself be reparative as a process, at least then and there, whatever may happen afterwards, when it has ceased.

As recovery is a true healing process, which begins

only after irritant actions have ceased, or nearly so, and could not begin so long as the damaging process of inflammation antagonised it, and itself is so distinct from inflammation, its nature, characters, and tendencies cannot be indications of those of inflammation ; and therefore it is not permissible to argue that inflammation itself is reparative because recovery is so. Yet is this line of argument sometimes used, if only by implication.

Recovery is indeed but a delayed repair, and like it is opposed by inflammation, which itself deals only with the events preceding recovery and demanding it. Between the two alternative theories here presented, I am therefore compelled to reject the one which says the irritant actions and irritations are cancelled by the responses they evoke, in the irritated and responding organism ; and to adopt, until a better one is demonstrated, that which says the irritant actions come to an end often in virtue of the normal developmental faculties or attributes of the parasitic irritant in animals, not less than in plants. This conclusion will stand, I think, at present as the best basis for a true appreciation of the beginning of a recovery in both kingdoms of nature, at least after parasitically induced responses to irritant actions.

§ 24*d*. So put, this theory of recovery is also in some degree applicable to the responses to irritant actions of a non-parasitic order ; which, although they produce less typical inflammations, yet do induce inflammation in very numerous, possibly the most numerous, instances in animals, though commonly they are the less serious ones, and so are the less specifically distinguishable forms ; and therefore are those which are less strongly marked off from the pure repair processes. In any case the responses to non-parasitic irritant actions obey the law of natural causation, are equal to their causes, persist as they do,

and cease when they do, just as is observed in the responses to parasitic irritants.

Thus, whether the irritant be a physical agent such as heat, a violent mechanical impact, or a series of slighter impacts, a chemical substance or an enzyme, its actions as an irritant are not arrested, nor is the irritation cancelled by the responses it evokes; but rather, in each of these groups, such irritant actions are brief or enduring, slight or intense, in accordance with the corresponding conditions of the agencies acting as irritants; all of which are extrinsic to the organism, or at least to its part, and all of which may endure or cease without material or constant reference to or dependence on the responses they evoke; so that the heat may be dissipated, the energy of the mechanical impact may be diffused, the chemical substance, perhaps a caustic, may be either evaporated, dissolved, diluted, or even perhaps changed by entering into new combinations, due at least in a very large part to its own intrinsic qualities. And recovery only then begins if and when these agencies diminish or cease to irritate through and by changes in themselves, however induced. Thus, in all these groups, each irritant may cease to irritate of its own accord; but in each case does so only after it has first and necessarily effected just so much irritation as by its own attributes it could do, and as conditioned it must do; and it is not shown that the responses evoked determine such cessation in any appreciable degree.

In considering these traumatic irritant actions, irritations, and the responses they evoke in higher animals, we must remember that they only so act as irritants when and as long as they so persist; that they must cease so to act if and when the irritant is removed, artificially or otherwise; that they, if not so removed, and if they are not

soluble or diffusible, they excite at least a local response, by which they are or may be encapsuled ; but they are not otherwise changed, as we can see in tattoo marks ; and that these responses are not a true or pure repair, but are inefficient compromises, in which the irritant is never cancelled, and is always operative in some, even if but a slight degree, which varies much in accordance with any casually attending pressure or tensions. Recovery, therefore, here also begins as the irritant ceases to act, and such cessation at least begins from causes not set up by or in the responses.

If necroses result, directly as passive effects of the actions of any of these traumatic agents of injury, or indirectly as results of irritant actions, which is very common ; and if these necroses remain non-parasitic, which is rare ; then we have to deal with a position of a somewhat different order, in which the necrosis or the necrosed mass often is, or may be, itself an irritant, though often a feeble one ; but it is not the original one, for that has often ceased to be or has gone, as has the agent of injury, and the responses are commonly due to complex causes, some of which are parasitic.

It is in a pure trauma, more commonly or chiefly, with irritations or disturbances of an intrinsic origin and nature, and with the responses to them, that an approach is made somewhat towards those phenomena which attend a repair of massive wounds, bruises, or crushes, in complex tissues in higher animals ; in which hindrances in the shape of clots and dead tissue débris delay a repair, and may even prevent it, that this question deals ; and here we are upon a marginal zone, a very important one, where perhaps more than elsewhere it is very difficult to say whether we are dealing with a pure repair or a recovery, or with some form of a mild but yet a true inflammation ;

and on this point I express here no very confident opinion, because the facts imply overlapping and admixture.

To make the position clearer, let us take an example, and imagine a small aseptic angular fragment of an insoluble, chemically almost inert, solid substance, say silica, in rapid motion, so projected that it produces a wound, loses its mass motion, is embedded in the tissue, and rests in the wound, we may assume, so that the orifice it entered by is closed by elastic contraction.

What in such a case can we, if the preceding views be accepted, expect will happen? We will assume that no later intervening septic or other irritants, even motions, complicate the problem. The wound certainly would tend to repair, in virtue of the evolved reparative faculties of the organism; but the persisting included fragment of silica would hinder the process, and in the area occupied by it would prevent efficient regeneration. Escaped liquid exudations and tissue débris would also hinder the repair. The local pressure or resistance of the fragment, and perhaps also the said débris, must set up some degree of irritant action in the nearer uninjured or less injured tissues. The response, therefore, is one of an inefficient attempt at repair of an injury, in which the agent of injury persists, and is a slight irritant. The response is necessarily, therefore, as much mixed as are the etiological factors. The reparative or regenerative responses would operate, deal probably efficiently with the blood-clots and tissue débris; but, under the conditions present of a persisting gentle mechanical irritation set up by the foreign body, would yield only an inefficient response, the scar-tissue of an encapsulating fibrosis, and not a complete reversion, or a resolution.

Such a response is, in a sense, an inflammation, seeing that it is directed somewhat by the irritation. But it

yields a product which in some degree may restrain the pressures of the impacted fragment; and it is possible for some pathologists to contend that such inflammation cancels the irritant, while it is, I think, more true to say that the reparative process is the restraining influence.

Yet does the fact stand, that the product of the responses, however brought about, renders the disturbing influence of the impacted foreign body less important, apparently in virtue of the exceptional density of the newly formed fibrosis or scar-tissue. It also stands, that this tissue is not a true normal connective tissue, not an unmixed product of a pure repair process, not a true or a complete recovery, which indeed could scarcely begin while the foreign impacted body persisted and appreciably irritated its environment; but it is a mixed product, a compromise, so to say, in which the reparative regenerative efforts operate, may even dominate the response; but in the presence of the persisting gentle irritation maintained by the fragment of silica, they are so modified that the product is not quite a normal repair, though it can persist and functionate for the affected organism with some degree of efficiency. The case I conceive of, as one of which, even in the presence of local irritations, if gentle and although persisting, the evolved reparative faculties can begin a recovery, but cannot carry it through to complete efficiency, because the agent of injury and the irritation persist in action sufficiently to make this impossible. In such a case, the irritant is not expelled, or even cancelled, for it persists in action; but the response does perhaps truly bear or suffer such action with less of perturbation than does a normal tissue. This example is but one, yet it fairly illustrates a multitude.

Some of these have close analogies with instances which have been given in plants, in which dead or dying parts

or inclusions are divided off by a protective layer from the living parts.

In some of these cases in higher animals, without doubt, phagocytosis is a factor of great importance, the exact significance of which I need not here discuss; although I scarcely hesitate to say that, in view of all the considerations involved in the study of inflammation, one cannot upon this basis erect a true theory of inflammation in general pathology; and one cannot say that here is an example of the cancelling, or expulsion, of an irritant by the responses it evokes.

Although I grant that such a view has some apparent plausibility, yet it is, I think, capable of complete disproof. When, as so often happens, a necrosed mass becomes infected with parasitic microbes, the irritations they set up both complicate and even dominate the responses, and then the casting off of a slough, or the separation of a gangrenous member, is not truly or simply a result of a non-parasitic inflammation, but it occurs as, at least in part, a result of a parasitic inflammation. The emigrated or other phagocytes have not yet been proven to be the true equivalents of such cell-proliferations and developments as both in plants and in animals form the encapsulating fibrosis, or the separating and defensive layers by which a dead or a foreign body is so often marked off from the living tissues near it; but neither have they been confidently shown to be not able to proliferate and develop.

In all the cases of inflammation, parasitic and not, the law of natural causation, which demands the equality of cause and effect, must obtain; and in no case is it shown, I would say indeed it cannot be, that the effects or the responses cancel, arrest, or expel the causes, acting as such, for this would be to prevent the effects,

which is absurd. True, it may be freely granted that, in all such causative actions and reactions, the causal energies are transformed, and are then represented in and by the effects; but this in no way conflicts with the law that $c = e$,[1] or sustains the doctrine that the responses cancel the irritants while they act as such. As in plants, so in animals, I can recall no example in which this law does not govern; and in no case is there any evidence known to me showing that the responses to irritant actions arrest them or expel the irritant, before it has done its proper work for the benefit of the irritant; in no case is evidence available to show that it fails to do such work, rather always the responses evoked represent the transformed energy of the irritant, and so are to be considered as its equivalent, under the conditions present.

Cohnheim's contention that the etiological factors are not important in considering the characteristics of the inflammatory responses is fallacious, in that it ignores the well-known trigger actions.

It is another matter, and one about which I will not here speak with a similar confidence, how far it is possible for the responses to irritant actions sometimes to benefit indirectly in some degree the responding organism. This point is to be answered in experience only, and I will not here enter upon it; but I can at least say that the responses do not forestall or prevent the action of the irritant, even if it be sometimes true that they in the end may help to a recovery or leave such an event possible, and may result in a repair, if and when the irritant has relatively ceased to irritate, because the irritant had always been economical in producing "injurious irritation."

§ 24*e*. In animals as in plants, recovery is always

[1] J. R. Mayer, *Die organische Bewegung*, 1845, and *The Forces of Inorganic Nature*, 1842.

effected by, or is represented by a regeneration of tissue like, or as nearly like as may serve, that necrosed or lost; and by replacing it, though often so imperfectly as to leave ample proofs that the outcome is but a compromise. This is what I would call recovery by patch; and as in very many inflammations, probably in all the typical forms, there occurs some necrosis, and the regeneration after it is very rarely, if ever, such as to exactly restore the original forms and structures as they had been, the result is a scar composed mainly of, or like, those tissues in or near the inflamed focus which are most amply endowed with regenerative faculties, to wit, chiefly the vascular connective or epithelium, and such a scar may be a larger or a smaller part of the final result, either well defined and separable therefrom, or so intimately mixed with the neighbouring tissues, and so like them, as to be indistinguishable in structure or in function. The product of this form of the recovery process is so like a repair of a simple injury in its results as to be distinguishable from it often with difficulty, if at all; and so it must be held to indicate again, that recovery is but a return to repair or a delayed repair.

In animals as in plants some uncertainty still exists, as to whether recovery by a true reversion to the norm of a cell or cell-complex after it has itself been irritated can then or later take place; at least this is, I think, uncertain for some of the cells. In animals as in plants it appears, however, probable that such reversion can and does sometimes occur; but then it may be only in those forms or degrees of "injurious irritation" in which the disturbance or perturbation from the norm of the cell-substance has been less profound, as, for example, at the periphery of an inflammatory focus, where such disturbance may well be thought of as less in degree, and where the proximity of

quite normal cells and tissues is also a factor, or in some cases where the whole focus has been but very slightly irritated; and then it may be without any necrosis coexisting in any part of it, as may happen, I think, sometimes in traumatic irritations. Satisfactory evidence that this reversion does occur seems to me wanting; but I incline to the view that it does occur, and I impute the deficiency of the proof in part to the great complexity of the problem, and in part to the fact that the point has received less attention than, as I think, it merits; and this provisional conclusion applies both to plants and animals.

However this may be, the fact stands that recovery in some mode after or from an inflammation is frequent, and is apparently often complete in animals; and if not more so than in plants, it is at least more prompt and striking.

Such instances as we see in higher animals of a rapid resolution, *i.e.* a reduction of local heat, and redness, pain, and swelling, almost to a norm, with apparent functional restoration, are to me unknown in plants; and in them I know of no examples which can be exactly compared with, say, a recovery after a lobar pneumonia in man, or an acute arthritis in some of the forms of the so-called acute rheumatism. The high degree of specialisation of structure and function seen in higher animals, involving as it seems to do their reparative faculties not less than others, may well explain this apparent superiority in the velocity at least, and possibly in the perfection of the recovery after some inflammations of these animals over plants. Such recoveries, however, can in no legitimate way be considered as proofs that in such instances as those given, or in any others, the responses themselves cancelled the irritant actions, or determined the beginning of recovery; rather, in these cases, also, the reasons already given stand as adequate grounds for the belief that the

parasitic irritants only then ceased to irritate, when their own needs and purposes no longer demanded of them so to change.

I will not here stay to discuss in detail the objections which might be made to this broad statement; but at a later period they will, I hope, be spoken of and answered. Now, I will only repeat the statement already made, that *Recovery* is not *Inflammation*, is only delayed *Repair*; and by its characters, those which characterise *Inflammation* cannot be distinguished.

§ 24*f*. Moreover, many of the cases in which the inflammation, although typical, is fleeting, *i.e.* soon and apparently perfectly recovers, seem to be due to the action of irritants which are similarly fleeting; often, it may be, they are traumatic and experimentally used, and in these cases, as the irritation had been slight and the disturbance or perturbation of the cell-substance trivial, it may fairly be said that, like the cases met with at the outer borderline of a better defined localised focus, some recovery by a reversion can and probably did there take place.

In short, it is both instructive and legitimate to consider the events taking place at the outer border of a severe but a limited focus of inflammation as closely allied with those met with in slighter inflammations, whether more diffused or not, of which, either we confidently infer or know from observation, that the irritants in action had been slight or evanescent, or both; and putting all these into one category, we may better comprehend them all. Such considerations have enhanced value, when we contrast and compare evanescent irritations with more persistent ones, if also slight, as is often seen in those due to a simple trauma, then yielding often a fibrosis with little or no previous necrosis, as after some prolonged exertions in working or in walking.

I will here reconsider a little more in detail the methods and mechanisms of some of those remarkably rapid and apparently complete recoveries from typical inflammation called recovery by resolution, and not presenting exact parallels in plants, as I have already said.

Take for an example acute lobar pneumonia, and note its tendency to end in recovery with only resolution, at or near the eighth day, by a series of steps which are very prompt and apparently always coincide in time with an equivalent cessation of the previous damaging, spreading, inflammatory and febrile responses. And note that, in the course of the spreading and damaging responses which characterise the earlier stages of the malady, we have some cell-proliferations, some emigrations of leucocytes, and accumulations thereof, some accepted increase in the numbers and activities of phagocytes of different origins, many and various circulatory disturbances involving exudations, serous and fibrinous, and these all coinciding in time and place with the growth and rapid multiplication and spread of the extrinsic irritants, that is, of the specific infective microbes which determine the malady.

The periodicity of the beginning of recovery, and its rapidity, are both frequent and marked, and need an intelligible explanation ; but this is not given by or in the doctrine, which has reached such a wide acceptance, that such recovery is largely due to the phagocytosis or to the active exertions of some other of the inflammatory responses, so as to cancel or expel the irritants which had determined them ; thus assuming that the emigrated leucocytes or the other phagocytes, although they are determined by the "injurious irritation," yet later on in some way cancel or destroy the infective irritant agents, englobe and digest them, without explaining how and

why it is that this later effect is so contrary to the earlier ones, if indeed it be truly an effect.

Yet, obviously it is inconsequent to contend that the same microbes at one earlier period excite inflammatory responses with very grave damage, and at another later one are destroyed or cancelled thereby, without assuming, as also necessary, some changes in the said microbic infective parasites, or in their conditions, which can reasonably explain these asserted and very different results. If, as I freely grant, phagocytosis is a factor in different parts of the long, complex and somewhat mixed process, in which at least some of the microbic irritants are or may be englobed, digested or removed, and is or may be so both in the earlier and in the later stages, I do not grant that it is shown to be one which appreciably arrests or cancels the inflammatory responses in their spreading stages; for were this so these stages could not develop, in this or in any other analogous or typical inflammation, which spreads and is locally or otherwise infective.

There is much more and better ground for the doctrine, that the individual microbic irritants in the earlier stages of the malady have but brief lives, or phases of life, and as they change in this regard, they may and do diminish or vary in their irritant activities in the part, and may then be dealt with by the phagocytes as are many other useless or perhaps very slightly harmful foreign bodies; and that the dead or dying microbes so often described as found englobed and perhaps waning in the phagocytes are such microbes which had already done their work as irritants, and were no longer important to the colony of parasites.

The later or spore stages of the same microbes are not yet shown to be, and are, I think, not so digested or destroyed by the phagocytes, even if and when they are

englobed by them; but they are then more probably removed or dispersed for their own advantage; and certainly they remain infective both to the same organism and to others, for the dispersed microbes or spores are virulent.

In any case, the argument by which this remarkable periodic and prompt recovery of a pneumonia by resolution can no more be imputed to phagocytosis as one of the items in the inflammatory responses than to some of the other particular changes seen therein, such as the cell-proliferations, the circulatory changes, the leucocytic emigration and liquid exudations of various kinds; any or all of which have been studied in this connection as means by which the irritation is often said to be cancelled, and recovery initiated; all of which are, in my judgment, incorrectly so thought of, and none of which have as yet been proven so to act.

Rather would I urge that all these responses to irritant actions, like the others I have above dealt with in animals, and in plants, are responses misdirected by the irritants in action, are fitly related to them during the earlier stages in which the responding process advances, and then that they tend relatively to diminish or even cease, when the irritant has reached a relatively resting stage, or is nearly fit to be dispersed, and then this change is for the sake of and related to the needs of the species of parasite.

In this way I would explain the actual observed facts in the markedly periodic, as well as rapid, beginning of recovery in pneumonia, as really dependent upon the arrival of the irritant microbes at a stage of development in which they largely cease to irritate, and then both seek and find, by the help of the host organism, the means of dispersal, whether by expectoration or in some other more indirect and circuitous route not as yet well understood.

That the host organism may indirectly co-operate in this provision for a cessation of the irritation, and for the dispersal of the progeny of the irritant, is quite in harmony with the views I have already advocated; but such co-operation is a part rather of recovery than of inflammation, although the two processes may often overlap; and it does not indicate any reparative effect brought about by the responses to the responding organism.

It is quite consistent with these views to grant that during the processes of recovery the phagocytosis, and I doubt not some at least of the other responses to the initial irritations, may at certain stages indirectly co-operate in helping to remove or even to cancel some of the effects of the actions of the débris of various kinds which had resulted from the regressive phenomena of the inflammation; but these events would belong more nearly to the reparative connections of the recovery process or to its methods and mechanisms than to inflammation proper.

In no case known to me is it shown that at any period or stage of the process of this inflammation, or of recovery after it, the spores of the irritant microbes are killed by or in it, or that their infective attributes are even impaired, as a result of it. Thus, after a pneumonia, not less than after other acute inflammations, *e.g.* a variola, a boil, or an abscess, the beginning of recovery depends largely upon the normal changes in the development of the microbic irritant, which in all cases at length escapes, is dispersed, and is virulent. It is also quite as significant, that during the initial and advancing stages of such an inflammation the same species of microbe which had acted as persisting and repeating infective irritants, and had in those stages determined the damaging phenomena of the responses in their specific and characteristic forms and varieties, so as always to be fitly related to and beneficent to the irritants,

had yet always survived, so that an ultimate dispersal of its infective germs or spores is adequately provided for by the suffering host organism ; but only if and when these microbes had ceased to act dominantly as irritants.

Therefore, in this periodic and striking recovery by resolution after pneumonia, its beginning must rather be imputed to the intrinsic normal changes in the irritant than to the inflammatory responses themselves ; for these latter began as consequences of the irritant actions, persisted and advanced in correspondence therewith, and were measured thereby, so that without the irritants the responses could not be explained, or indeed occur ; and it is quite beyond my comprehension to impute to the responses, without introducing some other and competent factor, their own cessation of action or their destruction ; especially when, as in the case here considered, strong analogies point to an intelligible explanation which harmonises with other natural and allied phenomena in animals and plants, and tells us also what the new and competent factor is. The interstitial character of the process of resolution, and the completeness of the recovery usually seen in these cases, are in some respects peculiar ; and these distinctions are not imputed to the inherent normal changes in the irritant, at least not directly ; for although these must precede the beginning of recovery, the changes referred to must rest upon the intrinsic reparative faculties of the suffering organism. Such an interstitial recovery or resolution is by no means constant in animals, and it is not known to me at least in plants.

§ 24*g*. In both kingdoms of nature the methods and mechanisms of the processes of recovery vary very much in different organisms, although among them all cell-proliferations, regenerations and developments are constant and necessary ; and yet always are such as to leave the diverse

textures and organs also in this respect free to diverge very much in connection with their own several reparative faculties.

Recovery, however, by resolution is by no means limited to a recovery after pneumonia, for in some degree and kind it is met with in the peripheral parts, at least, of many other inflammatory foci, after the irritant actions have ceased to dominate. Some such interstitial resolution is seen, for example, around many suppurations after they have burst, or are freely incised at a proper stage; after many serous inflammations or joint inflammations, as after acute rheumatism; and even after such acute specific inflammations and fevers as scarlet fever. Although in all these the diversities of method and of process above mentioned are very obvious; and they influence often in striking ways both the local tissues and the most widely distributed organs and parts, solid and liquid.

The investigation of such varied modes and mechanisms of recovery in animals, shows us some intermediate stages or phases between recovery by resolution, and recovery by scar-production, after a previous necrosis or destruction, however produced; as may be seen in the recovery after suppurations, and after slighter or more evanescent injurious irritations. And in animals, in some cases at least, there is reason to think that in recovery by resolution, or after slight or temporary "injurious irritation," an actual reversion may sometimes occur of an individual cell which had itself been only slightly irritated, to a normal condition.

The conclusion then stands, that recovery only then begins after inflammation in animals when the irritant actions have for some reasons relatively ceased; and this is a constant in all cases; but the periodicity of the beginning, its promptitude, and its methods, whether by resolution or otherwise, are not constant; indeed, these

vary very much with the organisms and the tissues involved, and there is no real and true close analogy in their nature between a resolution, or any other recovery processes as such, and the origin or beginning of the recovery.

In plants in this respect there are some rather important distinctions to be noted, so far as my reading and observations go; and it is convenient here to introduce a comparison, and give some examples. In them an interstitial resolution or a recovery by such methods is, as I have said, not known; a recovery by a true reversion of a previously irritated cell or tissue is rarely recognised, if at all; but a recovery by patch or scar is very common and complete.

A common currant-gall on the oak leaves, such as yields a *Spathegaster baccarum*, after having grown and developed into its specific form and structure, and ceased so to do when the gall-producer has rested as a pupa, and the gall has afforded facilities for the escape of the mature insect, dies and withers; and usually then, at or near its attachment, a repair by patch or a scar is formed, after the complete necrosis of the gall, by the help of nearer living tissues either only slightly previously irritated, or not so at all. Such a series of events is fairly comparable with that which follows the pointing and bursting of an abscess in an animal.

An Alpine rose gall, or that which is so common on the *Rhododendron ferrugineum*, and is due to the irritant actions, growth, and development of the *Exobasidium rhododendri*, is another and very instructive example; to which may be added an allied gall common upon the *Vaccinium Vitis idæa*, and some allied species due to the *Exobasidium vaccinii*. In these galls it is easy to observe the growth and development of the new gall in a constant and exact relation to the growth and spread of the Exobasidium in its earlier

or mycelial stages between and in the cells of the leaf or axes of the host plant, and of course also in a similar constant relation to the normal growth and nutrition of the host plant, followed by a cessation of such growth and development of the parasite and of the gall, just when the former begins to fructify and to cover the surface of the gall with the well-known beautiful and delicate layer of spore-bearing tissue. Then, as the earlier mycelial growth of the parasite ends, and its period of fructification begins, the whole gall undergoes a necrosis; the dead parts fall at length, and in some way a sort of repair by scar takes place, which is all that here stands for recovery. The two processes are clearly here distinguished; the earlier, that of the inflammatory response, as I say, ends, and the later then begins, and initiates recovery; and both stages or phases subserve the irritant in all its stages, including that of dispersal of the spores in an infective stage.

Neither of these recoveries—for as such they must be thought of—is strictly comparable with a resolution in animals, or with a true reversion, I think, in plants; but in the latter, if we observe the cases of slight fleeting irritations such as accompany some of the cecidia due to Phytopti, or to Aphides, which sometimes produce leaf-curls or pouches which the irritants inhabit only for a short period and then abandon; then we may find at least some of the peripheral cells and tissues near a focus very little modified by the injurious irritation, often apparently normally functionating after the irritants have departed; and then it is possible, or even probable, that some very slightly previously irritated cells and tissues may have reverted to a norm; and this seems to me to be the nearest approach to a recovery by reversion or by resolution which I have met with in plants.

§ 24*h*. In animals then, as in plants, typical inflammation itself, or its equivalent, never brings about its own recovery, is not itself a reparative or a salutary process, never cancels or expels the irritants or the "injurious irritations" in the parasitically determined forms, and there is no good reason known to me for saying that the conclusion is a different one for the non-parasitic inflammations.

In animals, as in plants, recovery is commonly initiated by the natural, even one may say autonomous or spontaneous, normal relative diminution or cessation of the irritant actions when the needs of the parasitic irritants require it, at least in parasitically induced inflammations. In the non-parasitic inflammations also, the responses, as in the parasitic, are measured strictly by the gravity, or the persistence, or the kinds of the actions of the irritant, as are other effects by their causes ; a truth which is well shown in the fleeting responses to slight or briefly acting irritant actions in all organisms.

§ 25. I pass now from the special attention so far here given to *Recovery*, and in some measure from the consideration of the series of events as limited to the nine heads before mentioned ; and will deal with some of the lower animal organisms, with greater liberty, yet so as if possible to include all the required essentials for the study in them of *Repair*, *Inflammation*, and *Recovery*.

In this section, typical inflammation in animals has been kept mainly in view ; and consequently, chiefly those higher vertebrates in which it certainly occurs and has been mostly studied ; and although some lower animal forms have been referred to incidentally, it has been mainly to elucidate in some way the conceptions of typical inflammation as here understood, and distinguish them from allied phenomena sometimes seen in other organisms.

However, it must be observed that, as the spirit of critical inquiry spread, attempts were made by analytical methods to better comprehend the steps or details of the several phenomena which together were held to constitute a typical inflammation; and to do so, the greater convenience for this purpose which the lower vertebrata, especially frogs, afforded, was seized upon, with results of very striking importance and value, but without resulting in any considerable changes in the general conception of a typical inflammation. The picture was filled in as to its details, especially those connected with the circulatory phenomena, but yet it had the same general aspect.

Thus, the area of observation for inflammation was expanded, so as to include at least all the vertebrata; and although in this way some of the phenomena which generally had been accepted were either somewhat ignored or were reduced to relative insignificance, *e.g.* heat and pain, yet no hesitation was felt in accepting the succession of changes shown in a frog's web during "injurious irritation" as exemplifying and helping to explain a typical inflammation as seen in man.

But the expansion did not rest even at the lowest of the vertebrates: the facilities for observation, and numerous other advantages of such an expansion, as well as the instructive and illuminating results thereof, gave a fresh impetus to investigators on these lines, and at length all invertebrate animals were included in the field for research, which thus became for many pathologists more truly comparative than it had been, at least in animals. Even some of the lowest of all organisms, which as yet are not with confidence classified either as animals or plants, and perhaps are more nearly related to the latter than to the former, *e.g.* the myxomycetes, were brought within the field of view, and within the terms of comparison.

This expansion to invertebrata also was too valuable in its results to be revocable, so that it remains with us ; and although, notwithstanding all the gains which have resulted therefrom, they have also been accompanied, as was the case in the expansion from man to the frog, with some necessary relative diminution of importance in regard to some of the previously accepted characteristic manifestations of the process of typical inflammation as seen in man and in frogs,—notably a great reduction, almost a complete loss, of the more obvious vascular phenomena, so well marked in vertebrates,—yet is the doctrine accepted by a large school of pathologists, not by all, that the manifestations, such as they are, of the responses to irritant actions seen in the invertebrata are inflammations or some equivalents thereof ; and if not typical inflammations, are yet within some part of an unbroken and continuous series of gradations with it, the reduced significance or absence of some events such as the nervous or vascular changes notwithstanding.

Within the wide limits of the animal kingdom this doctrine now dominates, perhaps, but it does not as yet go further, and extend to plants.

Necessarily thus, the extension of the field of view has led to modifications of the older doctrines, as to what, in a typical inflammation, is essential to and characteristic of it ; and here we at once meet with some very important divergences of opinion still prevalent, and some of which, at least, I am sustained by a hope of being able here to reconcile.

§ 26. Ignoring now some of the relatively less important results of the study of inflammation or of its equivalents in the invertebrata ; and also holding as less important, for the moment, the influence among invertebrata of such vascular and nervous systems as they,

or at least some of them, possess, and the contrasts of the processes exhibited in these vascular invertebrates, when seen in the non-vascular forms; it can be said that as a broad result, in such responses to "injurious irritation" as are most widely found, the vascular changes retire into a relatively back place; the proliferative changes come more forward, and then, as may be seen also in the non-vascular tissues of man, the proliferative changes are, if not the sole, at least the more constant, prominent and characteristic manifestations in the process.

Among the series of changes present as manifestations of all inflammations in animals, without doubt such proliferative phenomena are necessarily associated in disease as in health with at least an equivalent supply of growth-materials; and so the essentials of a vascular supply are always present; and in this way, the inclusion of the invertebrata, especially of the non-vascular ones, has tended to increase the relative significance of the cell-proliferations among the manifestations of inflammation, and to reduce the circulatory responses relatively.

In this way it has also resulted that the responses to irritant actions in the invertebrata are found to be manifested in modes which bring them nearer to those we have seen so markedly developed in plant galls.

It is, however, to be constantly borne in mind, that, notwithstanding the increased attention recently given to inflammations or their equivalents in invertebrata, they have not yet been studied with such fulness of detail, or success, as has typical inflammation, or, I think, even as the responses to irritation presented to us in plants. Perhaps partly for this reason, it has to be acknowledged that some diversity of view is apparent still, not only in regard to the general theory of what in the invertebrata is the equivalent of a typical inflammation, but as to some

of the facts observed, or rather as to the true significance of the appearances.

Thus, it may be said in regard to the local accumulations of cells, or of phagocytes, at or near a focus of "injurious irritation," the sources and significance of which accumulations may be open to discussion, that in every such case it cannot be questioned that a cell-proliferation has taken place somewhere in the same irritated organism; that it has then been related somewhat to the irritant actions; and that during the process of accumulation and by it some damage is done to the organism, whatever may happen afterwards.

It needs, therefore, no further argument to show that in all animals inflammation or its equivalent can be generally and rightly accepted as met with; but it remains a matter of controversy what is meant by the equivalent, in the invertebrata, of a typical inflammation as accepted in man or in frogs.

§ 27. As a contribution to the clearing up of this question, I recall to mind that the nine heads already spoken of in connection with typical inflammation in man and in higher animals all arise, and all apply in all animals, higher and lower, vertebrate and invertebrate, vascular and not; for all of them are liable to injuries, and to "injurious irritations," and all respond thereto, in modes varying with the extrinsic causes of injury, and of "injurious irritation," and also with the evolved intrinsic faculties of the injured or irritated thing; and from these some can recover.

As it may be said with much confidence, that within the said nine heads are included the essential problems of repair, inflammation, and recovery; and as in all the invertebrata all the same heads are presented to us for study, we may legitimately conclude that such of the

phenomena manifested in inflammation as are common to all animals, and are never absent in any of them, are the essentials, and so are the characteristics of it, because they alone are constant; and if this be so, then some form of modified and damaging proliferation of structural units, or of cells, or of both, is the constant we are in search of, for all inflammations in all animal organisms.

But this conception is not generally accepted, rather it is disputed or denied by most of the greater schools of animal pathologists.

Thus, it may be said, that in all animal organisms, if my views can be sustained, inflammation, or its equivalent, occurs in some form; and that the only form which constantly prevails is a proliferation of the structural units of cells, or of the cells themselves, or of both; but that in all cases it is so modified by the irritant acting disadvantageously for the responding organism, and at the same time fitly related to the irritant; so that, for the present at least, it is the only known constant amid the variable, in inflammation or its equivalent of any form in any animal; and by this character it can be recognised always as the response to "injurious irritation."

Can these views and statements be sustained? I think yes. They are disputed, I grant, and some of them are denied. But they can be, I think, established by observations in comparative pathology, in animals and plants.

Even some of those pathologists who have specially surveyed the whole field of animal organisms, including some of the organisms below the inferior boundary of animals, or at its ill-defined lower margin, and have compared the whole in a comparative study of inflammation, have been led to the conclusion that there does exist a break of real and grave importance, in the series of changes which animals exhibit when "injuriously irritated," and

dispute or deny the teaching that an unbroken series of such changes can be traced between a monad and a man in this series of changes.

Thus, Metchnikoff, although accepting the existence of inflammatory responses to "injurious irritation" in some invertebrata, and although contributing himself largely to the knowledge we possess of the actual changes seen in the lowest animal organisms as consequences of such "injurious irritation," denies that such changes can all be considered as inflammations, or their equivalents, or are in an unbroken series with that succession of changes, in the higher animals, to which all apply that term. He contends that, in animals below those which have or have had a mesoderm, inflammation or its equivalent does not occur, and cannot, because the mechanism which he thinks is involved in its manifestations is in them non-existent, not having been evolved. That is to say, the resulting differentiations of a mesoderm are not found in the lowest animal organisms.

His position is much like that of those pathologists who, conceiving of inflammation as necessarily and essentially a vascular change, are obliged to deny the possibility of its occurrence in non-vascular tissues, or in non-vascular organisms. He, as they, having first framed a definition, which is rigid and exclusive of some tissues and some organisms, is bound by it, even to the extent of leaving out of the whole theory some portions of the field he has surveyed, to wit, tissues and organisms of a non-vascular structure, and so also in his own theory all the lowest animals, or those without a mesoderm ; and this he does, while not denying that in these tissues, and organisms, also, some characteristic responses to "injurious irritation" do occur, for which no name is given to replace, or be the equivalent of, the inflammation denied, and he gives

no theory, or at least none of a satisfactory kind, by which such phenomena as are admittedly found are explained, or are put into a known category.

The responses are said to be not inflammation, and not its equivalent; and yet are they thought of as something which, if it were more developed, would be an equivalent of inflammation, or even that process itself. This or a similar unsatisfactory position is a necessary consequence of any definition of inflammation which is not comprehensive enough to include all living organisms.

Metchnikoff, however, although he indicates a decided break in the responses to "injurious irritation" met with in animals beneath those with a mesoderm, and separates them from typical inflammation, does trace some connection; which is conveyed in his view that inflammation is evolved like a normal faculty, and is seen at its highest stage of development in the highest animals, though not yet perfect even in them; and in the lowest, is so undeveloped that a distinct break can be traced at the point in the animal series where the mesoderm has not yet been evolved.

For him, then, I conclude that the responses to "injurious irritation" in the lowest animal organisms are not considered inflammation, only because in them the mechanisms which that process demands, in his definition of it, are not developed; but that in them "injurious irritations" and the responses thereto do occur he does not doubt, although these he gives us no name for, while he implies that they may represent or be equivalent to an undeveloped inflammation.

If his definition be not sound, or can be shown to be inadequate, this ground or reason for saying that a real break exists in the animal series, as to the kinds of the responses to "injurious irritation," fails. Also, if it be

shown that inflammation cannot rightly be regarded as a normal process, or as one which is evolved in animal organisms, is most developed in the highest and less so in the lowest, then also his view as to the said break in the series fails.

That his definition of inflammation is inadequate, at least for any satisfactory theory of inflammation in general pathology, is proven, I think, by its necessarily excluding an immense number, perhaps even a majority, of animal organisms, and all plants ; and also by its inadequacy as a satisfactory explanation of a typical inflammation itself as seen in man, in all his parts and tissues.

This I will not seek to establish in detail here, as the attempt to do so would be somewhat out of place ; and for the moment it must suffice to say, it is not proven, or even I think generally accepted ; and if this be so, it does not justify his assertion of the existence of the break he contends for in the series of changes after "injurious irritation" in all animals, by which the lowest are excluded, as well as all plants, from the field of view, and from the theory.

§ 28. That inflammation is not rightly to be regarded as an evolved and normal faculty, seems to me certain ; for although I fully accept the doctrine that not only all animals, but all organisms, plants not less than animals, necessarily possess, and have evolved by a survival of the fit, faculties both for repair of waste and of injury, I am not able to accept the doctrine which Metchnikoff propounds, that inflammation itself is also to be regarded as such an evolved faculty of repair, or as a salutary response to injury of any kind, for the fact that it is constantly more damaging than reparative in the focus contradicts this doctrine. And the established fact, that in every typical and other inflammation, so long as it lasts, and in pro-

portion as it is intense, damage is done in and by the process, proves that it never could have been evolved by a survival of the fit.

I therefore must reject this doctrine, deny that inflammation is itself a reparative process, or is an evolved and salutary faculty, and therefore this ground for the assertion that the lowest animal organisms which had not evolved a mesoderm are separable from the highest by a distinct break in the characters of the series of responses to "injurious irritation," and that in them neither inflammation nor its equivalents can occur.

Rather I hold that all the animal organisms, high and low, as well as plants, have been evolved by a survival of the fit, and have thus evolved truly reparative faculties which are efficient, and are known thereby; that these faculties are liable in all organisms to be perturbed by irritant actions, and then to be inefficient, and themselves to do damage in the process; and that then inflammation or some real equivalent thereof is present; but that such inefficiency of, or perturbation of repair, is not itself a faculty evolved by a survival of the fit, although the faculty of repair so perturbed had been so evolved; and that such a normal repair faculty varies in different organisms, and tissues of each, in kind and degree, yet is it altogether absent in none; but it persists as an active factor in and throughout the process of a response to "injurious irritation" even when it is perturbed, *i.e.* during an inflammation, although then it acts inefficiently and does damage; yet it is always traceable throughout all animal and all plant organisms, without a true or a real break, in any of its chief or essential factors; that is, in the evolved faculties of repair, and in the not evolved perturbations thereof.

But in regard to these last, it is always found that the

influence of the perturbator or the irritant is traceable as that which irritates and misdirects the intrinsic, evolved faculties of repair, which may or may not ultimately prevail, and recovery may begin; but if so, then only when and if the perturbator or irritant has at least relatively ceased from some cause, and no longer dominates or misdirects the responses.

So considered, inflammation, typical, or only seen as some equivalent thereof, cannot be itself an outcome of evolution by a survival of the fit; rather, it is a disorder or a casual disturbance of the evolved faculty of repair, and so it is always antagonistic to it. It is a true disease process, a casualty, and this is proven sufficiently by the constancy of damage present in all inflammations of every type and degree in all organisms, animal or plant.

§ 29. I need not therefore now hesitate to say that inflammation of some type or degree, or its equivalent, is met with in all animal organisms; and I venture to add that it should be considered as coextensive in animals with repair, of which it is a disorder or a perturbation, and that it is not to be confounded with the faculty which is perturbed, as Metchnikoff's teachings tend to do.

One result of the extension of the area of observation for the study of inflammation in animals is therefore to help us to bridge over the gulf by many pathologists supposed to exist between man and moss, in the responses to "injurious irritations"; and thus we are brought to the acceptance of all organisms as included in the area for the comparative study of inflammation.

Here it is expedient to reconsider the view I expressed at p. 16 of the Address (1893), "that the reactions of all living tissues to irritants are rightly considered as inflammations," and to point out that the passage had then a special relation to plants; but as it is followed by

another which says, "A general theory of inflammation should include all organisms," it applies to the subject-matter of this section, and so it includes animals. In the first section I acknowledged that this doctrine was not generally held, either as regards the first or the second clause; now I venture to say that it is tenable and well grounded in each of its parts. A verbal qualification is, however, wanted to make the meaning clear, namely, that "injurious irritations" should be the term used instead of "irritants," and so the doctrine should be, *that the reactions or responses to "injurious irritations" of all living cells or tissues are rightly considered as inflammations in all organisms, plants or animals.* So expressed, however, it is not explicitly stated that all the reactions or responses to "injurious irritation" in all living organisms are manifestations of an inflammation, or that such manifestations are set up only by "injurious irritation" and not by any other causes.

Yet is this view implied, it is tenable, and is, I think, in the main true. I grant that, as "injurious irritation" is a cryptic change, and is itself not appreciable by observation, and even the irritant cause of it may often be undiscoverable, so that the observer very often has to rely solely or mainly then upon the phenomena seen in the responses, in order to discover it; yet in animals particularly, pathologists have, I think on adequate grounds, accepted such evidences that inflammation was present; and they have been fully justified in assuming in these cases the previous or concurrent influence of the irritant and the "injurious irritation."

See for examples variola, scarlet fever, and syphilis in its various manifestations, and many other maladies, the number of which was much greater before the development of bacteriology. So that, given certain close

resemblances and analogies in the characters of the responses observed, inflammation was and is confidently diagnosed, and held to imply a concurrent "injurious irritation," upon the evidence of the manifestations seen in the responses; and thus, I think, is justified the whole of the above statement, if and when the said manifestations were truly characteristic of accepted forms of inflammations.

The second part of it is, indeed I think has been, herein further justified by the facts given, which go to show that no other known cause of or constant in any inflammation in any organism has been demonstrated. In animals therefore, perhaps even more distinctly than in plants, the idea of inflammation as a constant and necessary consequence and concomitant of "injurious irritation" seems to be well founded; so much so that, even although the latter is only an inference founded upon facts observed in a characteristic response, it is yet confidently inferred and accepted.

§ 30. If this conclusion be as well established as I think it is, it follows that all the disease-products which present to us the characteristic manifestations of inflammation, whether with or without any discoverable agent of irritant actions, or any "injurious irritations," are to be considered as inflammations of some type, whether or no they have hitherto been included in that category; and thus are included, I think, many new growths or so-called tumours; and this conclusion applies with especial force to the so-called malignant growths, whatever be the tissue which they begin or develop in, or spread to; whether it be epithelial, endothelial, connective, or any other; and whatever may be the grade of malignancy they present.

Such malignant new growths are often said to be distinguished, in part, by their autonomy of growth; but in this respect they are at least equalled by some benign

tumours, by typical inflammations, and they are indeed exceeded by some plant galls, *e.g.* those on the purple willow.

They are not separable from inflammations by their frequently, indeed almost constantly, fatal termination, by their infectivity, local or general, nor by the lines and directions or extents to which they spread, nor by the cells and tissues in which they begin and develop; for in this regard, like inflammations, they are met with in all cells and tissues which proliferate and develop.

Neither are they separable by the regressive and necrotic changes they produce, nor by the concurrent progressive cell-proliferations and developments they present, often in great excess and disorder—although this statement is much controverted.

Nor can it be said that they are distinguishable in their etiology, for this has not as yet been confidently made out for malignant neoplasms; and some authorities of weight, even among those who explicitly deny that it is parasitic, while they cannot and do not deny the local infectivity or at least spread of the malignant new growths, yet freely grant that some irritation, often thought of as chemical or mechanical, is sometimes an important factor in it; and such "irritation" must be "injurious."

Neither can it be said, that when studied comparatively in other organisms they are separable; for this study, although it has been carried on mainly in vertebrate animals, has not yet been adequately extended to the invertebrata or to plants with that completeness which enables anyone to say that any living organisms are free from such disease manifestations.

§ 30*a*. True, a recent report to the lay public, in the *Times* of July 9, 1904, by the Cancer Research Fund Committee, says that, as cancer has been found to pervade the whole of the vertebrata, and in them presents "constant

fundamental characters," so as almost to imply that in other living organisms it is not present, while granting that no *a priori* grounds exist for assuming that cancer may not be found in the invertebrata, concludes also that, as the vertebrata live under very diverse conditions of food, habitat, etc., such "external agencies have no causative influence."

This conclusion is certainly not warranted by the facts stated in the report, and it would, I think, be as justifiable to say, that "external agencies" have no etiological significance in the production of many typical inflammations, even the parasitically induced ones, which in many of their characters closely resemble malignant new growths, whether called cancer or not, as it is to make this virtual exclusion of all extrinsic causal factors, and the consequent limitation of the etiology to the intrinsic ones only, at the very beginning of an original research upon cancer and its causes.

The same report also says: "It is not permissible to seek for the causative factors of cancer outside the life-processes of the cells; and it has been possible by the experimental study of transplanted tumours to elicit proofs that these factors must be sought in these life-processes" —a conclusion which is as little justifiable as the previous one, of which it is a repetition in more precise terms.

§ 30*b*. However, an examination of the "Scientific Reports on the Investigations of the Cancer Research Fund Committee," No. I., 1904, by Dr E. F. Bashford and Mr J. A. Murray, shows their teachings more fully. In it they say (p. 10): "The wide distribution and identity of character of carcinomata prove that cancer is primarily based on the few conditions which are common to the forms in which it occurs, and only incidentally a problem of human pathology."

This may be true in the limited sense, that in all cases the excessive cell-proliferation, misdirected as it certainly must be by some thing or influence, rests finally upon the evolved intrinsic reparative faculties of the organism, in cancers as in other disease-processes and responses; but it by no means therefore excludes—nay, its acceptance, I think, demands—also an explanation of the initial misdirection, as well as of the local and general infectivity or spread, and of the malignancy, which are here not at all adequately dealt with, and apparently are not thought to be demanded.

So that it by no means follows that the extrinsic factors can be ignored in dealing with the etiology of cancer, even if this be limited to the conditions to which the organisms liable to it are exposed. Yet Bashford and Murray say (p. 10) that "the cytological and experimental investigations of carcinoma as a whole bear out this conclusion, and show that the essential factors must be sought in the potentialities residing in the cells which constitute the living body. The great diversity of the habitat, food, and conditions of life generally of the forms in which malignant new growths are found, relegates such external agencies to a subsidiary rôle, if they play any part whatsoever in determining the incidence of the disease."

Surely such great diversities of habitat, food, and conditions of life of the animals in which these growths occur also suggest that they may possibly be potent factors in their etiology, and by no means justify their exclusion to the extent here contended for.

This conclusion is somewhat less precise and explicit than that given in the report already quoted from the *Times*, as it does not say distinctly that "external agencies have no causative influence"; but in this form it is not warranted. Nor is the conclusion justified that the essential factors exist in the potentialities of the cells.

Bashford and Murray grant (p. 10) that "the characteristic common feature of the infective diseases is not the histological lesion, but the presence of the causative organism. In cancer the histological lesion is identical throughout, and at present constitutes the diagnostic criterion": and they add that the "artificial transmission of cancer is only successful within the species in which it has arisen."

In face of this truth, I find it impossible to make out from this report what is the exact significance of the expression "identity of character of carcinomata" used at p. 10, *l.c.*, for the histological lesion constituting the diagnostic criterion is not set forth or generally established. They apparently infer that, as no causative parasitic organism has as yet been demonstrated, for cancer none exists; or at least they do not refer to any; and implicitly, almost explicitly, deny that any such can be operative as an important causal factor.

The fact, as it with our present knowledge seems to be, that cancers can be experimentally propagated only in animals of the same species, although of value, does not serve, as they seem here to think it does, to shut out a parasitic etiology; for the fact is also known that some parasites are limited to single species of hosts, and determine in them characteristic responses.

They do not describe what is the identical histological lesion relied on in cancers, and accepted as a diagnostic criterion, and they assume, without giving evidence, that it is generally accepted in cancers as an adequate "diagnostic criterion"; apparently, not only for carcinoma, but also for all other malignant new growths, their enormous varieties in grades of malignity, sites and conditions, and the existing diversities of opinion upon the question notwithstanding; and they adopt this criterion

apparently without question; so that the "diagnostic criterion" upon which their whole investigation of cancer in animals rests is of no more real significance than was the histological "diagnostic criterion" of tubercle before the bacillus was demonstrated, or than the similar characteristics of variola and syphilis in man now are: that is to say, as significant, in the ratio of the closeness of the structural analogies they present to other inflammatory responses in which the irritants, parasitic or not, are known.

The histological diagnostic criterion of cancers here so completely relied on, is even less valuable than was the old one for tubercle before Koch's discovery; because Bashford and Murray use the term cancer very often as the equivalent of malignant neoplasms generally of any type; sometimes as the equivalent of carcinoma, thought of as a particular kind or variety thereof, limited to epithelial tissues; and sometimes, while recognising the constant persisting distinctions between the kinds of malignant neoplasms, as is seen in their study of the metastases, they refer their conclusions, as founded upon carcinomata, chiefly, though not solely, to other and very various types of malignant new growths, the specific characters of which are but little known, or not further than their histological characters, with some connection often with the physiological or anatomical types of the tissues in which they are found. So studied, the histological criteria of malignant neoplasms vary much, are less defined than carcinoma, and less than those of tubercle were before the bacillus was discovered.

In conformity with their general doctrine as to the intrinsic etiology of cancers or malignant neoplasms generally, they study with great care the cell-proliferations met with, especially the mitoses; while they neglect,

relatively at least, any inquiry into the initial etiology of these observed variations from the normal cell-proliferations, in the primary growth, direct or indirect, both of which they apparently grant, although they attach, as I think is legitimate, a higher importance to the indirect or the mitotic changes.

Consistently, as they have excluded all extrinsic causes of the changes observed, it suffices for them to investigate thoroughly the intrinsic phenomena, the causes of which they however ignore, or seem to think are given in the idea of intrinsic changes.

Having "in the first annual report pointed out that the investigation of the problem of the genesis of malignant new growths was regarded as distinct from the question of the conditions of growth," and adding that "on this basis a comparative study has been undertaken of the mitoses in the cells of malignant and benign new growths and in the processes of repair and inflammation" (p. 16), they did not, with these limitations, feel it needful to inquire much further than the details of the intrinsic phenomena ; and in any case, they have not adequately studied the genesis of the progressive proliferations, and their relations with regressive and other modifications, mitotic and not, in the primaries ; but only the details of these changes, however initiated, in new growths ; and also, in repair and inflammation, though in regard to these latter with less completeness, and apparently, at least, not in such detail as is, I think, required for proof of their views.

The remarkable, and indeed constant, association of regressive modifications with the progressive ones, and of both with malignancy, at least in cancers and other malignant neoplasms, has similarly received from them but scant attention, and no sufficient explanation. They

recall with appreciation Von Hansemann's work in regard to the abnormal mitoses in malignant neoplasms, and they note that in these new growths cell-divisions were observed with multipolar mitoses, often multinuclear in character, that there were also diversities in the amount of chromatin in the nuclei, and at times amitotic division; but these results are here given without any definite conclusion thereon being reached.

As a general result of an extended search into the infiltrating peripheries of malignant new growths in various animals, they say (pp. 16–18) "that the cells responsible for these processes conform closely to the characters of the similar surrounding tissues, both in their histological form and in the character of their mitoses." And they observed a tendency for multipolar mitoses also to occur there. Such abnormalities of mitosis and of cell-characters were studied by Von Hansemann in man, and described by him under the general term "anaplasia"; but Bashford and Murray say that although they accompany they cannot be made responsible for the malignancy in the new growths.

Von Hansemann grouped the variations in the mitoses he observed into those with the normal number of chromosomes, those with fewer, hypochromatic, and those with a higher number, hyperchromatic. He studied the modes of production of the hypochromatic mitoses, either by asymmetrical mitosis, or by a casting out, or by a degeneration of individual chromosomes. From such hypochromatic nuclei there arose sometimes nuclei with a higher number of chromosomes, in some ways not clearly explained. He did not find or give a constant number of chromosomes either in the normal or the hypochromatic nuclei; the numerical reduction was therefore variable, and was quite unlike that met with in the

history of normal reproductive cells. He associated these, and some other changes in the mitotic figures, with the altered biological characters of the cancer cells; and he was, in fact, apparently content to find the steps of the process, without inquiring further into their initiation. He opposed the parasitic theory, even if he did not explicitly declare against all extrinsic factors in the etiology of cancers.

Bashford and Murray confirmed Von Hansemann's statements as to the occurrence in malignant new growths of hypochromatic nuclei, *i.e.* nuclei, with fewer chromosomes than normal; and in part his two modes by which the numbers of chromosomes are reduced, and also the occurrence of the hyperchromatic nuclei, in their researches, which were comparative.

Bashford and Murray, in this connection, considered the paper by Professor Farmer, Mr Moore, and Mr Walker (*Proc. Roy. Soc.* vol. lxxii.), who investigated cancers in man and very carefully the earlier stages of the hypochromatic nuclei, concluding that the reduction in number of the chromosomes took place in the same way as it occurs in the ripening of the spermatocytes of animals, and in the spore mother-cells of plants: who also found that the numbers then "were approximately halved, as compared with those of the somatic mitoses" (p. 19). And, noting that "in the maturation of the gametes of animals and plants, bivalent chromosomes appear as rings and tetrads," add that "the resulting mitotic figure is characteristic and is known as the heterotype."

This result is, say Bashford and Murray, a unique phenomenon in the normal life-history of organisms; and this association of bivalent chromosomes, with their reduction in number to half the somatic number in malignant new growths, is, they hold, a fact of very great

pathological importance. They also, in a paper read at the Royal Society, confirmed this observation of the occurrence of bivalent heterotype ring and tetrad chromosomes, in malignant new growths in other organisms, such as dog, mouse, trout, cat, horse and cow. But they failed to find this remarkable change in the cells of the stroma of a carcinoma which were somatic in type.

They found that in these heterotype mitoses, the chromosomes were in many cases reduced to exactly half the somatic number, and they add: "The occurrence of a series of nuclear changes in malignant new growths throughout the whole extent of their known distribution parallel to those characteristic of the maturation of the sexual elements of the metazoa is a fact established beyond doubt" (p. 20).

A difficulty arises, however, in comparing the relations of the series of changes in the nuclearplasm and in the cytoplasm, in the sexual elements during maturation, with those met with in the malignant new growths; and it appears that whereas, in the former, the relative proportions and structures of the cytoplasm and nuclearplasm are constant and characteristic, in the new growths this is not so.

In this respect, then, cancer cells differ from the cells of sexual tissue. Some of the differences found between normal, *i.e.* sexual heterotype mitoses, and malignant ones are described and figured by Bashford and Murray at pp. 21 and 28, but no well-grounded conclusions seem to me to be derived therefrom.

In the course of this investigation, it should be noted that heterotype mitoses are met with in cancer cells which are, at least in part, degenerating, and in this way, *i.e.* by degeneration, Bashford and Murray explain the frequent non-development of the heterotype amphiaster, but no

explanation is given of the degeneration. I must call attention here to the remark by Bashford and Murray (p. 22), that "in estimating the significance of the heterotype mitosis in malignant new growths, however, the mode of its occurrence must be considered, and the established nature of the local origin, mode of growth, dissemination and power of differentiation, of cancerous tissues borne in mind" ; and I must also comment thereon, that we know not "the mode of occurrence," or the "established nature," or "the mode of growth," all of which are questions under investigation, and so should not be, as seems herein to be the case, assumed.

Bashford and Murray grant, that "all the cells of a malignant new growth do not undergo this series of changes" (p. 22), that is, the heterotypical ; "many undergo a differentiation into elements with the characters of the mature form of the tissue among which they arise."

This proliferation of cells, with differentiation into forms like those of the newer normal tissues, does not, as they assert, at all justify their position that the cancer cells alone proliferated and differentiated. The nearer tissue cells, may and I hold often, or indeed in carcinoma always, do so grow and develop.

It is more noteworthy, in regard to my question, that the number of cells undergoing a heterotype mitosis varies in different malignant tumours, is not constant and does not include all ; being small often in tumours of slow growth, and not always numerous, often indeed the reverse, in tumours in which a rapid cell-growth is present. The number varies even in the descendants of one and the same tumour, at different stages in its metastases, and in the daughter tumours, as when transplanted into a mouse.

In short, this heterotype change is not a constant

throughout the process, does not measure it, and of it "a direct relation to the degree of malignancy has not been established" (p. 22).

Further, "the mitoses encountered in the growing margin are uniformly of the somatic type, even in the multipolar figures thus far observed in this position" (p. 22).

Again, "in some cases, where rapid degeneration is a characteristic phenomenon, heterotype mitosis may be difficult to find" (p. 22).

They add: "These considerations militate very strongly against the value of the heterotype as a diagnostic criterion of malignancy" (p. 22). And it is obvious that the heterotypical change is far from being a constant one in malignant new growths.

This is true and important, and yet, what we want is an explanation of the etiology of malignancy, and of the degeneration and the regressive changes; for these characteristics are very constant in the whole series, and are remarkable in their constant association with progressive changes.

Bashford and Murray give us very careful records of their own comparative observations on heterotype mitoses in cancers, so as to enable them to be recognised; and as a prelude, note that the mitotic figures of the normal body in repair, and growth, are all somatic, and that the same is true of those met with in various animals in the processes of repair and inflammation, although of this they give no details in proof. They note that "the number of chromosomes in a somatic nuclear figure is constant, and is determined by the union in one equatorial plate of the male and female pronuclei, during fertilisation of the egg" (p. 24). But it must be remembered, that such somatic nuclear figures are frequent in cancers, and

their own figures are taken therefrom. They note that this number is retained during the mitosis by the equal division of the chromosomes longitudinally.

They distinguish the heterotype mitoses from the somatic by three characters: the chromosomes are not V-shaped loops, but rings, ellipses, or tetrads; the number of chromosomes is half of that in the somatic mitosis; and, in the amphiaster stage, the chromosomes do not project laterally beyond the spindle, but lie with their long axes parallel to it. There are also some distinctions when the chromosomes are ring-shaped, etc. They note as an important fact, that "the heterotypical mitosis in the maturation of the sexual elements of the metazoa is a definite stage occurring prior to fertilisation" (p. 29). Once this heterotype mitosis is complete, the subsequent mitoses in the nuclei continue with only the half of the somatic number of chromosomes.

In the malignant new growths the heterotypical mitoses in the nuclei are seen with diminished and, indeed, often only half the somatic number of chromosomes, without it being possible to find exactly how the diminution in number took place. In these heterotypical mitoses the chromosomes conform, however, strictly to the somatic type in their forms, direction of splitting, and arrangement on the spindle, and are known only by their half number.

On the ground, then, of this similarity of pathological heterotypic mitoses, with those of normal reproductive tissues, Farmer, Moore, and Walker concluded that the cancer process consisted in a transformation of the normal adult tissues into a modified reproductive or "gametoid" tissue, which possessed the features of malignancy; and that the absence of provision for casting off the continuously formed elements accounted for the continued growth in size and for the destruction of surrounding tissues.

In this conclusion no attempt, apparently, was made to show what the transformer was or is; and the authors (Farmer, Moore, and Walker) belong, it would seem, to the school of intrinsic etiologists, or at least they very much ignore the extrinsic factors in the etiology, notwithstanding that the environment is never absent, and is never inoperative, and the combination of intrinsic and extrinsic factors is, I think, always constant and necessary.

But Farmer, Moore, and Walker (p. 30) also say: "What seems to emerge from a general consideration of the whole range of facts is this, that in the higher animals and plants the post-heterotype tissue, with its own independence of organisation, does behave towards the surrounding tissues of the parental individual as a neoplasm. So far as the parent is concerned the new growth might be described as a pathological one, did it not form a normal stage of the life-history of the species." Thus in effect they deny that a malignant neoplasm is a pathological product!

Bashford and Murray controvert this teaching, largely on the ground that transplanted sexual tissues have no such power of independent growth and invasion; and as they find no close analogy in the facts of histology or of experiment, they definitely reject it, I think legitimately, on many grounds.

They also attach weight, I think too much in this connection, to the fact, that sometimes two independent, or at least distinct, malignant new growths may coexist in the same individual, and one may even invade the other, as each does the host tissues; and they hold that this fact shows at least that the difference between reproductive or sexual tissue, and somatic tissue, is not alone sufficient to explain the behaviour of malignant new growths towards the host and to each other.

Had they studied the galls within galls set up by

Synergi, and not excluded all extrinsic influences from their ideas of the etiology of malignant neoplasms, these tumours invading each other, or the host, could be otherwise explained ; and it interests me here to note that Farmer, Moore, and Walker, as well as Bashford and Murray, freely make use of plants in their investigations, when and if they seem to fit in with, or conform to, their general views.

The latter ask (p. 30), "By what peculiar process does an isolated group of cancer cells give rise to a new growth with powers of proliferation like those of the tumour from which it was derived ?" and they add that, were this question answered, much that is obscure in the nature of malignant tumours would be cleared up. No doubt it would, but the tacit assumption in the question is not justified, and I think parasitism here is strongly suggested ; and if all the facts and analogies be weighed, its importance is such as to demand much more attention than is here given to it. It would render needless the assumption that the isolated group of cells of a cancer themselves are efficient causes.

But Bashford and Murray have previously excluded all environmental or extrinsic etiological factors from the very foundations of their research, although it is an etiological one ; and they are thus limited by their own previous judgments to the intrinsic causal factors, which, essential as they are, cannot be the sole ones.

As they have given no definition of, or any adequate diagnostic character of malignancy, important though it is, as almost the sole known constant character in the whole group they deal with as malignant neoplasms ; and as they have in no way separated such malignancy as they deal with from the malignancy which is as real, as fatal, and as well or better known in many infective inflam-

mations; and as they have here given no attention to or definition of their idea of inflammation of any type; and as they have, here at least, not defined their ideas of neoplasms as a whole, or of the autonomy so often seen in tumours, and also, as I hold, in some inflammatory responses to irritations; they are not in a position adequately to state or answer their own question, nor, I think, even to discuss it with a good hope of finding an answer.

How strictly Bashford and Murray have previously limited their field of view, is shown by their statements at p. 15, where, after referring to the conclusions reached by the study of the zoological distribution and comparative nature of cancer, they say, "that the latter line of inquiry has led to the conclusion that the elucidation of the problems of cancer was to be sought in the potentialities of the cell itself, and the nature of the transmissibility of cancer reduces the field of inquiry to the cell again, and leads one to seek for the peculiarities in the cell life of normal and cancer tissues which limit the power of independent existence in the former, and raise this power to the level of being the chief characteristic of the cells in the latter."

§ 30*c*. In this passage an abnormally changed condition is accepted in the cells, and the cause of such change is left without investigation, as if it were of no account, or were as intimately related to the characters of the individual, or the species, as are the normal evolved intrinsic reparative faculties, that is to say, as if the abnormal were normal. Bashford and Murray not only sever their study of malignant new growths from all extrinsic influences, and thus limit it to the intrinsic faculties of the cells and tissues; and so also sever the initial causes of the changes of the cells and tissues

which are etiologically essential for the primary growth from the conditions or causes determining the peripheral, local, and metastatic spread of the malady; but they also hold that such spread, especially as it is shown in transplantation experiments, can adequately be studied apart from, and independently of, the initial cause of the primary new growth. In any case, this severance is arbitrary, and it needs a complete justification, which is not given.

They endeavour to sustain it in various ways, and in part by adopting the now widely taught pathological doctrine, that all malignant neoplasms grow and spread only by an extension of their own materials, independently of any co-operation by proliferation or otherwise of the cells or tissues of the affected organism.

But this doctrine does not, I think, rest upon an adequate basis of established fact; and at least if, as I grant, some facts can be adduced in its support, it has also some difficulties to surmount which have not here been duly considered. It is not altogether in harmony with their own statement (p. 16), "that as a general result of a general study of growing and infiltrating surfaces of many malignant new growths from various animals, the conclusion was arrived at that the cells responsible for these processes conform closely to the characters of the similar surrounding tissues, both in their histological form, and in the character of their mitoses." Neither does it harmonise well with their statement (p. 22), in respect of many of the cells of a malignant new growth, that "many undergo a differentiation into elements with the characters of the mature form of the tissue among which they arise."

This whole question is one of great complexity, and of equivalent difficulty to decide upon, and I cannot here

attempt to discuss it in detail; but I venture to urge that the confident assertions now so generally made by many pathologists, that malignant new growths spread in the suffering organisms as do parasites, and only so, need more proof than has yet been, so far as I know, afforded—at least, if we at the same time take due account of the difficulties which such a doctrine has to meet. I freely grant, that in some, if not equally in all, malignant new growths, the metastases grow and spread in the new sites, *e.g.* in a liver, somewhat as grafts do, and so as to show there histological structures like those of the primary growth, and often unlike those of the new site; but I do not grant that in such, and allied cases, this is a proof that the metastatic growth takes place only out of the materials of, that is, only out of the cells and tissues of, the metastased focus itself, as does, say, a tubercle bacillus, or a cysticercus, or a trichina; and I contend that the new growth in the metastasis, as in the primary tumour, does not, as the parasites do, derive only liquid growth-materials from the host; but also, as in the most characteristic malignant neoplasms which this doctrine deals with, that is, in the carcinomata, may derive a large, even an essential, part of them—to wit, the vascular stroma—by a demonstrable series of steps of cell-proliferation, from the similar tissues near by. And this fact is but one among many allied ones.

I cannot accept as adequate the explanation given by many pathologists, that the vascular stroma in a carcinoma is not a part of the carcinoma itself; but is a product of an inflammatory response in which the epithelial carcinoma cells are the irritant causes; and I call attention to the facts, that the said stroma is constant and necessary in a carcinoma; that it shares the fates of, and in the main measures, in each tumour the progress of it in all its

stages and grades; that so it really is inseparable from the epithelial growth; and if it be due to a process called inflammation, such process is at least a constant and an essential part of the carcinoma; even if it be, as is generally, and as I think wrongly, taught, that the whole response is not an inflammation, as I hold it to be.

I note also, that the stroma of carcinoma is not strictly a normal connective of the part, is not shown to be only an inflammation fibrosis, and is not as yet demonstrated to be differently related to the epithelial proliferations near, than are other associated tissues of different physiological types in health and in disease. In short, it is an essential constituent of the new growth, and is as necessary to the epithelial growth as dermis is to epidermis.

It can scarcely be urged, that in a simple, benign, horny epithelioma the process by which it grew was complex—that is, was an intrinsic one for the epidermis cells and extrinsic for the stroma; nor can this be urged for the slightly malignant warts so closely related; and if this be so, the most malignant carcinomata must, I think, stand in the same pathological category.

§ 30*d*. I may not here pursue the train of thought thus suggested, by the argument and the facts, into the wide range of malignant new growths not included in the carcinomata, such as the various forms of sarcomata, the endotheliomata, the adenomata, the lymphadenomata, and the little-known groups of malignant teratoid growths; but I may say that they at least prove in their structures that all the cells and tissues from, and in which, they spring, can in some way and by some causes be induced to begin a process of malignant new growth, in which the stroma is not shown to be, in its nature and kind, incapable of, or exempt from, participation, any more than are other tissues and their components.

On the whole, it may, I think, be said, that an extrinsic irritant influence, parasitic or not, but probably specific for each variety of a primary malignant neoplasm, is suggested as probable. This statement, however, is by the way only, and I rest my argument also as much upon the harmony or conformity which such a suggestion affords to the general conclusion reached by Bashford and Murray, and quoted above, from p. 16, as upon the want of harmony therewith shown in the growth of true parasites.

Moreover, I do not grant that all metastatic foci, even in carcinoma, are set up in the same way; nor that in all cases the transposed fragment is a separate mass or a group of cells, nor even always a whole cell in all cases; and this contention is, I think, highly probable, when we remember the diverse modes by which it can be shown that the infective parts or particles of a malignant tumour are transferred and distributed in or by lymph or blood channels, the limitations of our knowledge as to their earlier phases, and the greater attention which has been given to the larger or blood-vessel carried fragments or grafts. So that it is at least conceivable, I would even say probable, that a metastatic focus springing from a transposed mass of tumour tissue, may grow and develop in the new site, somewhat differently from that of a focus developing at a distance, and in a different surrounding tissue, from a viable, perhaps minute fragment of a cell, containing possibly a parasitic germ or spore, or perhaps some other irritant influence. Note in this connection that some malignant neoplasms metastase by the help of the blood-stream apparently as do some sarcomata, with a remarkable tendency to a bilateral symmetry.

Such apparent similarity of the histology of the metastases of malignant neoplasms with that of the primary

growth as is granted, does not necessarily exclude, therefore, the possibility of metastatic distribution of the same neoplasms by and through the influence of included parasitic or other irritants, which might indeed very well explain the phenomena. For many true, even typical inflammations, also metastase, and in general character, at least, the metastases resemble the primaries in histological structure.

I will mention here, although I must not dwell at length on the fact, well and long known, that the malignant neoplasms, both primaries and secondaries, infiltrate at their peripheries, in this respect resembling many inflammations of the most malignant types ; and I contrast this with another significant fact, that benign new growths, and also the larger or massive parasites, have a well-defined, and not an infiltrating boundary, while the microbic parasitic inflammations for the most part in this particular resemble the malignant new growths.

§ 30*e*. In considering the value of the evidence for and against the doctrine that malignant new growths grow in new sites only as parasites do, and only out of their own materials, I think the advocates of this view have not fully taken both aspects of the case into account ; have, in short, concluded too readily after considering only the apparent tendency of some of the factors involved, and have neglected duly to weigh all the difficulties ; so that in this way their conclusions have been, I think, inaccurate. Although I am obliged to grant that the consensus of opinion on the point is so strongly adverse to me as to be almost overwhelming ; yet, consensus of opinion is not a proof, and it has in the past sometimes been wrong ; although I feel that to resist it is a mark of presumption.

It is instructive also to note, that at this late stage

no other or better diagnostic criterion for malignant neoplasms is given, than the histological one ; and this is not as yet well defined ; it seems not to be contained in the mitotic changes here dealt with, which are explicitly said to be no measure of the malignancy ; and although in a sense Farmer, Moore, and Walker are disposed to think the heterotype mitosis is a true characteristic of malignant neoplasms, yet it seems certain that it is not constant in them, is not met with in all parts of them, may be absent even in rapidly growing parts, and so, if it be a characteristic when present, it is not a measure, and is of uncertain value as a diagnostic. I do not feel sure, but I think Bashford and Murray do consider it when present a diagnostic character, although not a certain, a satisfactory, or a complete one, which indeed it cannot be unless constant.

In this connection it must, however, be remembered that the mitoses in malignant neoplasms are irregular and very much disordered ; and that the heterotype forms occur, and are admixed with amitosis, homotype, hypochromatic, and hyperchromatic mitoses ; with nuclei, in which the chromosomes are half the somatic numbers, some in which they are less, and others more than half ; and it seems certain that they occur also in intermediate numbers ; so that when the exact half number occurs, it is not shown that it does so as an essential or certainly a constant phenomenon ; and it may therefore possibly be a casualty, amid such a variety of irregular changes. This view, however, is not entertained by either group of authors, and I do not press it, other than as a possibility to be remembered.

In conformity with their general views, and I may perhaps say prepossessions, Bashford and Murray carried on their investigations into the changes in the cells with

great care and exactitude, and found, as they thought, not indeed evidence of, but presumptions in favour of the idea, that the nuclei of the cancer cells sometimes conjugate, although they do not say that this is a frequent, and still less that it is a constant, phenomenon. They say at p. 31 that "the two nuclei become continuous through the cell wall," and "the process is identical with the process of conjugation in many protozoa and lower plants, and probably has the same significance—namely, that of starting a new cycle." They also add (p. 34): "It is to be hoped that similar observations in other tumours will soon permit of a final decision as to the occurrence and significance of this phenomenon." So that they thus clearly admit that it is not as yet widely or generally established; but they seem to show a bias. They conclude that, were it established, important consequences would follow; and this is true enough, but until it is established such consequences do not come in. And they say (p. 34): "Conjugation or fertilisation in all living forms is the starting-point of a new generation in protozoa and metazoa, in animals and plants. It is always followed in normal cases by renewed and independent growth, and is thus capable, without postulating anything, of explaining the independent growth of malignant new growths, and their metastases." Of course this presupposes the constancy of the conjugation, which is not established, or even yet asserted; and it is without justification to have said, as in the statement above made, that nothing is postulated, or at least assumed; for the causes of the asserted conjugation and of its beginning, though necessary for any clear thought on the matter, are left without explanation or comment, and yet are they tacitly postulated, in the malignant new growths, which show such conjugation.

Although such postulate is not needed in normal conjugations or fertilisations, it is, I maintain, quite essential in these abnormal conjugation phenomena; for the causes in these cases are not directly traceable in the evolution of the species.

It is not without an important relation to this problem to recall the fact, that normally in nature, among animals and plants, particularly I think among parasites, new life-cycles do sometimes begin without any known, near, or immediately preceding conjugation, or fertilisation; that for many successive generations, organisms, especially in their early stages and in the lower forms, are multiplied by fission, and budding, and parthenogenetically, and even heterogenetically, without any known immediately preceding sexual preliminaries or any at present to me known heterotypical mitoses or conjugations.

This fact is itself, I think, outside question, and it applies strongly to the whole series of responses to parasitic "injurious irritation," and to the beginning of some new growths, at least in plants. However, Bashford and Murray say (p. 34): "Whether a conjugation of cells or of nuclei of normal tissues is the initial phenomenon in the cancer cycle must be settled by further investigations; but it is certain that such a conjugation would explain, without further assumption, the characteristics of malignant tumours, their local but occasionally polycentric origin, their independence and behaviour as a new organism, their power of invasion, their differentiation in the direction of the mother tissue, the phenomenon of artificial transmission with all its limitations, and the superaddition of malignant properties to the tissues of those complicated tumours which are undoubtedly of congenital origin." And this doctrine all rests upon the postulate or assumption of conjugation as a constant, and so as a cause

of malignancy, which assumption is not at least proven, or as I think justified.

Occasional conjugation of the nuclei of the cells of cancers cannot therefore be used as a reliable histological diagnostic criterion of malignant neoplasms; and we are still without one upon which confident conclusions can be based, for nothing constant is known.

To this, their final conclusion, they add in a footnote the remark, that "these characters mark the malignant new growths as new organisms, morphologically and physiologically equivalent to the parent one which they are invading." By way of comment I repeat that the conjugation is not proven, except perhaps as an occasional, not a constant factor, in a very irregular and abnormal series of changes, in the histology and mitoses of the growth; that, if it does occur and is a constant, it must have a cause; that such cause is not given, and cannot be duly conceived of apart from the environment in which the organism exists, and by which it is always and necessarily in some ways influenced and conditioned.

Even if it be true, which is not proven, although it is here confidently declared to be certain that the characteristics of the new growths would be adequately explained by the conjugation, if it existed with the potentialities assumed, it is not a complete or satisfactory explanation, unless it relates such heterotypic mitoses, and conjugations, to their causes, of whatever kind they may be or from whatever source they may come; and it is not proven or *adequately* here attempted to be shown that such causes cannot be some extrinsic influences in the environment, parasitic or not; nor is any adequate explanation given or attempted, of the very real and close analogies shown by and in malignant new growths, and some of the well-known inflammatory responses to "injurious irritations,"

both those of which as yet we know not the irritants, even in the higher animals, as well as in some, especially in plants, of which the irritants are known.

Bashford and Murray are clear, or at least positive, in the view (p. 13) that "the process is in no sense an infection, the tissues of the new host not participating in the formation of the new parenchyma." The word infection is here used by them in a technical, restricted, and even perhaps unusual sense; and the non-participation of the cells of the new host or tissue in the cell-proliferation is positively affirmed without, as I think, any sufficient justification, or at least not such as can establish a negative. The use of the word infection here adopted by them is, I grant, rather widely held, but is not always accepted, and it is certain that authors, even those who use the word so, find themselves driven to employ it in dealing with the spread of malignant neoplasms, at least as a local process, which is not and cannot be pathologically limited.

§ 30*f*. Bashford and Murray say (p. 16) that "in the first annual report it was pointed out that the investigation of the problem of the genesis of malignant new growths was regarded as distinct from the question of the conditions of growth." No doubt, the two questions may be studied separately, however connected they in fact are; but this does not justify their complete separation, nor does it show a real independence; nor can one so support the conclusion drawn, that the genesis of the primary neoplasm may be left out of the investigation, or that it is not related to the "conditions of growth," *i.e.* of the spread of the tumour, as Bashford and Murray have in this conclusion asserted.

However, they say (p. 16): "On this basis a comparative study has been undertaken of the mitoses in the

cells of malignant and benign new growths and in the processes of repair and inflammation." I dispute this "basis of a comparison," and I deny that the genesis of malignant new growths is here shown to be distinct from, and not closely, even necessarily, connected with their conditions of growth, and modes of spread; and I dare to add that a genesis such as is here assumed to occur without cause given, is unknown, in fact, to any exact observations in nature, and is to me quite unthinkable. It rests upon no known or strictly analogical phenomena in nature, and yet it is assumed, and then expanded, so as to profess to give an explanation of the actually observed phenomena, of their extensions within, and outside of, the organism involved; and it does so arbitrarily, without proofs, and is therefore no real explanation.

I demur to the assumed basis of comparison also in large part, because in it, at the outset of an etiological research, one important group of facts, the extrinsic ones, are excluded from the comparison; and as the intrinsic ones are the sole alternatives, no true comparison remains possible, for one of its two terms is arbitrarily excluded in advance, and the excluded factors have been and still are believed to be essential by an important school of pathologists.

The further and equally unproven hypothesis, of the production of a "new organism" by a process almost equivalent to an abiogenesis, or at any rate to one of a spontaneous heteromorphosis, founded upon an assumption of an uncaused genesis, also affords us no intelligible explanation of known facts. The suggested production, somehow, of a "new organism" within a previously existing one, yet certainly, as it is granted by Bashford and Murray, in its genesis arising out of, and due to some modifications of its cells and tissues, without the inter-

vention of any extrinsic influences derived from the environment, is a unique instance; it is not supported by any known or truly analogical facts, and so it cannot be accepted as having any greater weight than a speculation, not well founded on facts. Obviously also this hypothetical new organism can even less than the mitotic and allied changes in the cells serve as a histological diagnostic criterion of malignant new growths.

The spread of the malignant neoplasm within the affected organism, or beyond it, without any connection with, or persistence of and spread of, any causal agency, like that which the law of natural causation demands for its genesis, but which Bashford and Murray elude or evade, is to me unthinkable. But I grant that it is not therefore shown to be impossible. Yet, they assert that in the peripheral infiltrating parts of the malignant new growths, the new cells (p. 18) "conform closely to the characters of the similar surrounding tissues," and, I dare here venture to add, are probably in some ways derived from them by cell-proliferation with modifications, even if and when the modes of such derivation have not been demonstrated.

This admission notwithstanding, they contend that the growth and spread of the suggested, indeed, almost assumed, "new organism," takes place as does that of a truly independent parasitic organism, out of its own tissues and tissue elements only; granting, I cannot doubt, some dependence at least upon the liquid or dissolved growth-materials of the host organism.

This contention is, in fact, now in some form very widely supported by those pathologists who hold that all malignant new growths increase and spread locally and generally by cell-proliferations of their own elements only, and not by determining any such proliferative phenomena in the tissue elements of the affected organism.

This doctrine, I think, is not at all so firmly established on facts as it is confidently asserted ; and it is even in conflict somewhat with the quotation from Bashford and Murray given above (p. 18), and also with some of the teachings of many pathological authorities, especially the older ones, and a few of the more recent ones.

There remain still some pathologists who maintain the view, that, whether or no parasitic irritation is a constant in the genesis of all malignant neoplasms, yet is some chronic irritation so, at least in some groups thereof; and thus they imply in such cases some cell-proliferative responses which must be closely related to inflammation, as it is here understood. And this view holds even in the face of Lubarsch's conclusions, which are on the whole strongly adverse to the parasitic theories, although his position is qualified somewhat. See his *Pathologische Anatomie und Krebsforschungen* (1902).

Some pathologists also there are who maintain that parasitic organisms can and do irritate and determine the genesis of at least some malignant new growths, co-operate in, and are effective in their growth and extensions, and whose views have not as yet been refuted, even if they are not yet demonstrated or generally accepted.

I do not intend here to re-enter upon this very important discussion ; but I may repeat the view that the complete exclusion of the stroma from any important significance in, or as a part of, carcinomata ; and its frequent and confident explanation as only an inflammatory response to the irritant actions of the epithelial growths ; asserted to be the sole essentials, is very much open to criticism, and I cannot accept it ; but hold that the epithelial elements and the stroma, or its equivalent, are as necessarily and mutually related each to the other

as are the dermis and the epidermis in normal tissues, and as are many other tissues and tissue elements in a complex organism constructed of mutually interdependent parts.

§ 30*g*. Still less is the general doctrine tenable, that all the varied malignant new growths can be adequately explained by the studies as they have here been carried on in carcinomata, which by no means all apply adequately to sarcomata, endotheliomata, and to many other varieties of malignant neoplasms ; yet is this general doctrine implied in this report.

Indeed, a disposition is shown by Bashford and Murray to attempt an explanation of all malignant new growths mainly from results which have been reached by a study of some of them only—often of those which are most convenient for observation, though not necessarily always the most instructive ; just as so many pathologists have attempted to explain inflammation by the results of its study in man ; and the outcome of such a restricted method of investigation of cancers, although it is often called comparative, so far, I think, has been as futile.

The outcome of this criticism of the first "Scientific Report on the Investigation of the Cancer Research Fund" is that : (*a*) it evades or ignores one primary, and as I think essential, question of the genesis of the morbid change in the primary growth, and excludes thus all extrinsic factors from the etiology ; (*b*) that it invents or assumes the production of a "new organism," which is neither proven nor tenable ; (*c*) that it in effect denies the persisting influence of the primary cause of such genetic change in the primary growth, in the spread and metastatic extension of the new growth, at least as an extrinsic influence, by assuming its absence, or by ignoring it ; (*d*) that it asserts without adequate proof, and in opposition

to much valuable teaching and some facts, the non-existence of any proliferative or other responses by or in the affected organism, in the extensions or spread of the new growths, due to any "injurious irritation" of extrinsic origin, derived in any way from the environment; (*e*) that it bases the investigation upon arbitrary exclusions or assumptions, which are neither proven nor justified; and thus, although in a sense an etiological research, it is not so pursued as to promise us much that is both new and true.

Let me add here that the report by the Cancer Research Fund Committee is in a sense official, its teachings are thus liable to be assumed as orthodox, and that therefore their validity is of greater importance to establish or refute. Here I am obliged to take the latter position, and this may perhaps excuse the length of this examination, in which I seek to show that an etiological research is carried on so as to exclude *ab initio* some essential factors.

§ 31. I feel, therefore, justified in still maintaining that at least malignant new growths are more intelligibly explained as inflammations—that is to say, as responses to some "injurious irritations," and most probably to parasitic ones.

In this way can be explained, I think, better than by the hypotheses advocated by Bashford and Murray, the phenomena seen in malignant neoplasms; to wit—(1) their genesis in the primaries, as due to extrinsically derived irritant agents of some and various kinds, not as yet satisfactorily or completely demonstrated: (2) their spread, extensions, and dispersals, as seen in nature, by the persisting or multiplying specific agents of extrinsic irritation, continued from and allied to the initial, genetic, and causal ones: (3) the fundamental dependence of such inflammatory responses, as of others, upon the evolved reparative faculties of the affected organism, which present

to us the intrinsic factors in the etiology of these neoplasms as of other inflammations, and explain such close conformity as is found in malignant new growths, with the normal tissues near, and out of which they grow: (4) the regressive or degenerative, and with these also the progressive and proliferative phenomena concurrent and commingled; which they like other inflammations present, as consequences of the misdirections by the extrinsic irritant persisting in action; and so I would bring them into a single series, within which are found, in many gradations, close analogies; and I do not place them as unique or disconnected events or phenomena in nature, and assumptions are not thus demanded without at least some, I think, adequate justifications: (5) that they do not show us any distinct relations of fitness with any known irritant cause, is granted, as may also be said of many other, and generally accepted, inflammations in which the irritant is not as yet satisfactorily isolated and studied; even in some cases of bacterially induced responses; and more so in those where the irritant and the irritation are only inferred from the characters of the responses, as in variola or syphilis: (6) in this way of dealing with malignant neoplasms as forms of inflammation, the definition of which is herein implied, but will be given, there is no imperative need for a separate definition of malignant neoplasms, or, here at least, for the so-called benign tumours—a difficulty which has led Lubarsch and others into some confusion, as he shows when he says no true tumours have yet been proven to be due to parasitic irritations, a statement confuted by and in the growth of many plants galls; and also by the cases which he himself conditionally accepts for some excitants of cancer, when co-operating with chronic irritation or embryonal remnants.

§ 32. A very few words must suffice in regard to what are called non-malignant or benignant new growths, in regard to inflammation, or the responses to "injurious irritation."

Excluding here all those neoplasms which have, even if only in a slight degree, any malignancy, and also now those which at some later stages, perhaps by some admixture or complexity of the etiological factors, may become so, I would consider all as benignant which are products of responses made by the evolved intrinsic reparative faculties to some past injury, or abnormality of repair; the origin of which is commonly not known. Often it may have taken place in an early phase of the life-history of the responding organism; and it must soon have ceased to persist in its actions, whether these were at first truly irritating or not. Thus a lipoma or a fibroma would be thought of here as a sort of deformity, or a product of a reparative effort, in which a bad compromise had been brought about, after the initial agent of injury had ceased to be directly operative. Each is related therefore to an imperfect recovery, and also to a malformation; and they as a group will be referred to again in connection with the teratological phenomena.

This conception of most benign tumours, although the adjective word so much and commonly used is linguistically useful and even needful, does not demand that we think of all tumours as benign and malignant, or as members of one common category; and it makes Lubarsch's expression, "echter neoplasm," needless, as not indicating any really existing natural group of phenomena, which includes all malignant and all benignant tumours. It conceives of malignant new growths as inflammatory responses to extrinsic specific "injurious irritations"; and most benign new growths as persisting effects of or responses to

injuries of many, and as yet unknown, kinds; in all of which the agents of injury have ceased to operate directly, yet leave some of their effects persisting, as we see in scars, after some recoveries, deformities, and in some malformations.

It severs the malignant from the benignant neoplasms in their etiology, as in their processes, in their fates, and in their classification.

Thus the inflammation idea, taken in connection with the recovery processes, can without material qualification include all new growths, malignant and benignant.

SECTION IV

THE INFLAMMATION IDEA, IN ALL ORGANISMS, IN GENERAL PATHOLOGY, STUDIED SO AS TO SHOW THE MUTUAL RELATIONS OF THE FACTORS INVOLVED, IN THE THREE GROUPS OF ACCEPTED FACTS, THAT IS, IN REPAIR, INFLAMMATION, AND RECOVERY

§ 33. As *Inflammation*, or something equivalent thereto, for which as yet no other convenient name is available, must therefore be accepted as presented to us in all animals, and as the nine heads under which the problems can adequately be dealt with, have been found and studied both in animals and in plants, the question must be more closely followed out, whether *Inflammation* or its equivalent is really met with in all organisms.

My answer to it must be unreservedly affirmative ; but this view is not the prevalent one, which is the conception of *Inflammation* as present in some form only, in some animals, and not in plants. In justification of my position, let it be remembered that in the examination already made of the nine heads, which collectively include the essentials of *Inflammation* and their equivalents in both plants and animals, it is shown that all organisms are liable to injuries and repair them, are liable to irritant actions and respond thereto by an inefficient and damaging effort, the manifestations of which present important

characters in common in both kingdoms of nature, especially in regard to the etiological relations of such manifestations with the irritant; so that it is justifiable to think of the efficient responses to injury which we know of as repair, both in plants and in animals, and of the inefficient and damaging responses to irritant actions, which we also know of both in plants and animals, together, as parts of one and the same greater group of very closely allied phenomena.

This inefficient response to irritant actions, or *Inflammation*, is terminable, and it often ends in recovery both in animals and in plants. As by common consent, the efficient responses to injury spoken of as *Repair*, are held to be the same in essentials in plants as in animals; and as there are, I venture to say, equally cogent reasons for speaking and thinking of the inefficient or damaging responses to irritation as also in essentials the same in the two kingdoms of nature, and as recovery is met with as widely, the position is, I hold, tenable, that both orders of response occur in both kingdoms of nature, that is, in all organisms.

In this way, *Inflammation* or its equivalent is rightly thought of as present in all organisms, and in general pathology; and this is, I hold, the only true view of the process. It follows that, if all the inefficient or damaging responses to "injurious irritation" in animals be accepted either as *Inflammation* or its equivalent, the same should be accepted in plants, unless good and sufficient reason can be adduced to the contrary. No such sufficient reason has yet been afforded for the more or less assumed break in this respect between animals and plants.

§ 34. Metchnikoff, however, makes this break absolute, and he does not grant in plants, as he has done for the lowest animals, and even for the myxomycetes, the occur-

rence in them of some as yet undeveloped approach to an equivalent of *Inflammation*. He says (*The Comparative Pathology of Inflammation*, p. 41, 1893): "We do not however find processes analogous to the essential phenomena of inflammation in the vegetable world"; yet he recognises that plants not only repair massive injuries by cell-proliferations, but respond in a closely allied mode to irritant actions, saying (p. 41, *l.c.*): "As in the healing of wounds, infections in plants are accompanied with regenerative phenomena dependent on the rapid proliferation of the cells that are not directly affected." So that he accepts normal repair in plants as in animals, and cell-proliferation as its manifestation in both; but he rejects absolutely the view that, when a somewhat similar cell-regenerative proliferation occurs in or near an infected focus of a plant, *i.e.* in or near an irritated tissue of one, it is even "analogous to the essential phenomena of inflammation."

It seems clear, that in this way he refuses to consider the cell-proliferation in a plant part, where it is infected, as in any way the equivalent of inflammation in animals; yet for him also, an infected part of a plant is an irritated part; and that the cells proliferated in or near that part are modified and disordered in arrangement is beyond question; but this observed difference between the cell-proliferations of repair in plants, and those which accompany infective irritation in them, he does not attempt to explain or to give a name to, and he contents himself with denying that it is in any way analogous to the essentials of inflammation as seen in some animals; or therefore that it represents an equivalent in plants of inflammation in animals. Thus, the locally excessive, disorderly, and damaging to the host, cell-proliferations, seen in or near an infected or irritated part of a plant, are left by Metchnikoff both unnamed and unclassified;

and they are not for him inflammation, nor even in any way analogous to it, nor are they any equivalent of it; and the only expression he here uses, by which his view as to their real significance can be gathered, is that in which he speaks of them as "regenerative phenomena." He uses this term here, I think, in the sense of progressive proliferations. If this be in a very limited sense true, it is not less so, that in no case is the product efficient as a regenerative one; and in every case it is as damaging to the host organism, as are other responses to "injurious irritation" in plants or in animals.

In the quotation given above, he is certainly wrong in the statement which implies that only the cells of plants which are not directly affected by the irritant proliferate.

The contrary of this has been demonstrated by Beyerinck and others, who have studied the origin and development of the gall-plasm from cells which have not been subjected to massive injuries, but have been to irritant actions. Metchnikoff appears to me on this point to have had in mind only, or mainly, those cases in which massive injuries or wounds were present, as well as irritant actions; and to have too little regarded those in which an irritant acted alone, while yet it has determined very marked and even characteristic gall-growths; although such cases frequently occur.

His disposition to trace inflammatory responses in animals to massive injuries chiefly is also often shown, and is in harmony with his views in regard to plants.

His absolute rejection of plants from among the living organisms which respond to irritant actions by a process analogous to or equivalent in any degree to *Inflammation* in animals, as he defines it, is, however, mainly due to the fact that, by his definition or conception of *Inflammation*, they in his view cannot possibly do so.

His theory of *Inflammation* demands phagocytosis ; and this he does not fully grant ever does occur in plants. I rather think on this point the facts are against him ; but I am not sure, and will not here pursue this question ; as it may be granted that phagocytosis is certainly much more highly developed in animals than in plants, even if it be granted as occurring in some of the embryonic stages, and in some of the lower forms of the latter, as in the plasmodia of the myxomycetes.

It must suffice for me here to say, that it is not a legitimate order of procedure to fix the theory first, and then to fit the facts thereto, as Metchnikoff has done very much in his study of *The Comparative Pathology of Inflammation*. Had he indeed said at the beginning of his inquiry, that his comparison only extended to some animals, his logical position would have been much more defensible ; but this he did not say ; and indeed he did take plants into his field of view for comparison, with the results above given ; and these involved his adoption of a theory of *Inflammation*, which in his view fitted the facts, though not even then in all animals ; and he did not consider that the non-inclusion of some animals, and of all plants, was a very serious or even a fatal objection to his theory, in its relations to general pathology.

Whether or no such a partially applicable theory of *Inflammation* be tenable within its own restricted territory, I will not now inquire in detail ; although I may note that it is widely disputed, and also that, as it is confessedly only applicable to some animal organisms, it is not a satisfactory theory of *Inflammation* in general pathology, as I understand and here use that expression.

Were it generally established, as at present is not the case, that *Inflammation* is a process only met with in some organisms or tissues ; and were a satisfactory explanation

given also of the phenomena, which seem to point to something as the equivalent of it in the remaining organisms, which also has at present not been given; it might, I grant, be proper enough to think of *Inflammation* or its equivalent in, or as a part of, general pathology, even although it were shown not to be present in all organisms.

I confess to feeling some want of clearness as to what Metchnikoff really teaches in regard to phagocytosis among the lowest plants; and how far he regards these as presenting to us, in a very low grade, an undeveloped phase of some equivalent of *Inflammation* somewhat comparable with that which he suggests as existing in the lowest animals without a mesoderm. On this point he is to me obscure, but his expression, in the quotation from p. 41, *l.c.*, that "in the vegetable world" we do not find "processes analogous to the essential phenomena of inflammation," seems conclusively to show that he makes an absolute break between some animals and all plants in this regard, which break is wider and deeper than that he contends for between higher and lower animals.

I now venture to say that the difficulties raised by Metchnikoff to the idea of *Inflammation* or its equivalent as a process met with in all organisms are not valid; or are not such as should prevent our accepting it, if on other and valid grounds it can be supported.

Most of the systematic writers on animal or vegetable pathology rather ignore the question I have just been dealing with than explicitly deny the occurrence of *Inflammation*, or an equivalent thereof, in both kingdoms of nature.

Animal pathologists in great part confine themselves to the phenomena of *Inflammation* of which the type is given in man, and use the lower animals only for particular

points or questions, for the solution of which they seem to be convenient ; and their theories and definitions are for the most part framed so as to include only animals, or some of them ; yet they are not all so framed as by their terms even implicitly to exclude plants, or indeed any living organisms.

§ 35. Some theories of *Inflammation* are so comprehensive in terms as to leave them in their application open to all organisms, *e.g.* Burdon-Sanderson's "the succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality" (*The Process of Inflammation*, 1871).

Some are such as implicitly must by their terms exclude all plants and even many animals, *e.g.* Cohnheim's, in which he asys that *Inflammation* essentially consists in a particular change in the walls of the capillaries and small veins ; contending also that the process of *Inflammation* is in all cases a disturbance of the circulation, and is the same essentially, let the causes of its onset be what they may ; so that he regarded the etiology as a valueless criterion for the classification of *Inflammations.*[1]

Phyto-pathologists, also, have mainly, almost exclusively, concerned themselves with plants, and, so far as my reading goes, have contributed very little to the discussion now before us. Rather they have dealt with the phenomena as seen in plants when irritated, as if there were no analogous or allied or equivalent phenomena met with in animals. From them, therefore, my contention derives no aid ; but it meets with no important opposition.

[1] Cohnheim's statement (1882), in this connection, that "it is an old and a trivial experience that different causes can have similar results," is misunderstood or wrongly applied, for the well-known trigger actions do not conflict with the law *Causa Æquat Effectum.*

The general trend of pathological opinion is now, however, so strong that *Inflammation* is limited to animal organisms, and indeed only to some of them, that this is for me perhaps the most important objection to be met in an endeavour to ascertain the liability of all organisms to that succession of changes, or to some equivalent of it.

Yet, giving here all the weight fairly due to this difficulty, and after a candid re-examination of the problem, I feel now compelled to reassert the opinion I expressed in 1892, and to contend that all organisms not only repair injuries, but also suffer perturbations of that repair process, and thus present us with a damaging series of changes which should be regarded as a true *Inflammation*, or at least an equivalent of that process, however varied it may be in its manifestations.

Some justifications of this doctrine I have already attempted to give, but I will extend them in this and the succeeding section. The acceptance of this broad teaching, however, although I hope to be able to show that it would, by enlarging the field of view, tend to improve and even correct some of the current views, would also demand considerable changes of doctrines long held and still dominating, in the theories and in the definitions of *Inflammation*; and particularly it would necessitate the rejection of all the theories and definitions thereof which are not comprehensive enough to include all organisms, but either explicitly or implicitly exclude some, or some parts thereof, and this largely because such theories and definitions are inadequate for a conception of the idea of *Inflammation* in general pathology, thought of as it should be, as coextensive with general biology.

While, as has been said, the general trend of pathological teaching has on the whole been adverse to, or has

given no support to this doctrine, it is a comfortable reflection to me, in thus venturing to contend for a view so opposed to much of the current teaching, to recall the fact, that some very great authorities have advocated it, or some approach to it; and, if not in all cases explicitly, yet implicitly, have given some support to its main contention; and some others have so carefully avoided framing their theories and definitions as to conflict with it, that it is fair to suppose its possibility was held in view.

§ 36. To some of these authorities I will now refer, and claim whatever of support their teaching may give to the doctrines here maintained.

Take first Virchow, and, without inquiring here who were his precursors in this field of inquiry, note first that his *Cellular Pathology* (1858) teaches that the living cell is the essential responding thing for all organisms, in physiological and in pathological states, and thus for him general pathology is coextensive with general biology. In *Die Cellular Pathologie* (fourth edition, 1871) he says (p. 4), "The cell is the true organic unit"; and again, "The cell is in fact the ultimate form-element for every living phenomenon, as well in health as in disease, and from it arises every vital activity"; and again, after guarding himself against the possible imputation of conceiving of life as something mystical, and completely distinct from other cosmic energies, he says, "However much the nutritive interchanges of material which occur within a cell may be bound up with particular constituents of it, yet the cell is always the seat of the activity, the elementary region upon which the kind of activity depends, and it retains its significance as a living element only so long as it persists as an essentially unimpaired whole."

Virchow's views of inflammation harmonised entirely

with his teaching of pathology in general, and with his dictum, "Omnis cellula e cellulâ." His theory of inflammation was a comprehensive one, and was not formulated within any very strictly limited definition, such as could exclude any organisms, or parts of them, if living. He disputed the adequacy and correctness of such restricting theories and definitions as were put forward by other authorities.

He thus claimed for plants, as for all other organisms, that they too respond to irritation by cell-proliferations, and he recognised the close analogies of such responses with those observed in typical inflammations as seen in the higher animals.

While maintaining that cell-proliferations were always in all organisms factors of the highest importance and constancy in *Repair*, and in *Inflammation*, he did not fail to teach that other modes of response also were important, even if less constant and universal in organic nature; and he held that, although cell-complexes and tissues, such as vessels and nerves when present, took a large, even sometimes an apparently dominant, part in a typical inflammation, yet for him were these forms of response not constant even in the higher organisms, in all their parts; as he showed by his references to inflammation in the non-vascular tissues of the higher animals.

He emphatically asserted that a true typical inflammation is met with in non-vascular and in non-nervous parts and tissues of higher animals; and yet is it also present in the vascular and nervous tissues, often quite near by, in a somewhat different form, but yet as the same thing in its essentials.

If he did not speak quite so explicitly and definitely of *Inflammation* in plants, his whole teaching supports the view that in them also it, or its equivalent, is met with.

In the first edition of the *Cellular Pathology* (1858), as well as in the fourth (1871), he speaks of inflammation, tubercle, cancer, and of sarcoma and other neoplasms, in such close relationship with repair and with gall-growth in plants, as to show that all these forms of proliferative response to injury and to irritation were by him regarded as connected by some common bond, into one and the same great group.

He neither in his survey separated plants from animals, nor the lower animals from the higher, nor the so-called tumours from the typical inflammations, such as are seen in suppurations. But, in so far as the organisms consisted of living cells, with faculties by which they responded to injuries and to irritants in action, and in so far as the diseases and disease-products spoken of were due to irritation, he thought of them as all in the same greater category as that which included both *Repair* and *Inflammation*.

It is very common to find pathologists, since the date of the publication of Virchow's *Cellular Pathology* (1858), who avow their acceptance of his dictum, "Omnis cellula e cellulâ," and this is so even among some of those who, explicitly or implicitly, deny that *Inflammation* is met with in all organisms. But it is difficult to find any who accept the wider general conclusions which flow from that dictum, as Virchow did. For the most part they are accepted only with qualifications, which vary legitimately with the other pathological views of the author, and have commonly for one effect the exclusion of some organisms, both animal and vegetable, from a liability to *Inflammation*; and thus often exclude also some of the cell and tissue responses to irritation, even in higher animals, from the great group of pathological phenomena to which the name *Inflammation* is commonly

given; which responses Virchow himself did include in the process as he understood it.

None of these pathologists, however, exclude any organisms from a repair of injury, or from tissue regeneration. They adopt the formula, but not its consequences.

This qualified acceptance is seen in a wide-spread disposition to criticise or contest his views as to irritation, and the cell-proliferative responses thereto; and also in an equally well-marked tendency to exalt the circulatory and nervous changes or responses and their collateral results, whether the emigration of leucocytes or the phagocytic phenomena, to a position of relative predominance, or even of exclusive importance, in the processes of *Inflammation*. See Samuel, *Der Entzündungs-process* (1873, p. 89), who says, "There is no irritant, no inflammatory irritation"; and also Landerer, "On the Doctrine of Inflammation" (Volkmann's collection of clinical lectures, No. 259, p. 7), who would drive out the word irritant ("Reiz") from the teaching of *Inflammation*, and says, "I believe that it has been harmful long enough therein"; and also Cohnheim, who in his lectures (1882, Bd. ii., p. 272) adversely criticises Virchow's doctrine of irritation, especially in regard to its conception of attraction of growth-material, and in relation to pus formation, and says it is an asserted *ad hoc* conception in physiology, for which no analogy exists in nature.

In short, the dictum of the "Master" has been accepted in form, but its spirit has not been accepted; or at least, it has not led many of Virchow's successors to the same broad conclusions to which it led him, in regard to *Inflammation* and its equivalents, in all organisms. The old tendency to limit the idea which the word *Inflammation* conveys to certain traditional and obvious local and striking series of changes, met with only in some

organisms and some tissues in them, has survived; and it has tended to limit the idea of *Inflammation*, considered as a process met with in all living organisms, to restrict it to some of them only; and thus it has conflicted with the dictum as Virchow himself understood it.

His want of success in applying his views to the particular case of pus formation may, I think, in part explain this fact; and doubtless also Cohnheim's rediscovery of, and brilliant researches into, the emigration of leucocytes contributed, perhaps largely, to a retardation of the acceptance of Virchow's views; although their foundations were not shaken, and the newer teachings did not long stand without challenge.

However, I may say that the "cellular pathology" is now as a whole firmly established, and if it be rightly understood, it carries with it the evidence that *Inflammation* or its equivalent is met with in all organisms. For this reason, largely, I venture to deal with it here somewhat more at length.

§ 37. Virchow rests his pathological teachings upon physiological facts and doctrines. He conceived of life in all organisms as a somewhat similar common property of them all, exhibited in their activities, and implying always the possession by them, though not exclusively in each of them, apart from their environment, of faculties which can only be manifested when they are under the influence of a certain stimulus or excitation from without. So that every living activity presupposes such an excitation or stimulus, or in other words an irritation ("Reizung").

This irritation, thought of only in its physiological aspects, he held, produces a passive change in the living substances of cells, such as never arrests their activities or destroys them. It induces, he thought, an active change, a positive product, or an exertion of a function of the living structural elements, varying with their intrinsic faculties, which are indeed thus manifested.

Irritability is thus evinced in a cell, and is the criterion of the life of an organism or of a part of one; but he fully recognised that it differs much in kind and degree in different structural elements, and that it is at times, here and there in parts of a living organism, not discoverable.

He attached great importance, both physiologically and pathologically, to the intrinsic kinds of activities, due to the irritabilities of the organism, or of its parts; and divided them into three groups, related to the function, the nutrition, and the formation thereof. He considered separately the various manifestations of these irritations in the tissues in man, and carried them on so as to include the emigrated leucocytes, the phagocytes of different sources and their voracities, so as, in fact, in some degree to have anticipated Metchnikoff. But he kept a firm grasp upon the idea, that the responses set up by the irritation are determined very largely, if not solely, as to their characters by the intrinsic faculties of the responding things; that they are, in short, as yet normal; and he does not indicate here any acceptance of the view that they are modified in any way by the irritant, which is for him apparently only a stimulant.

He insisted that in all cases the functional responses, even in pathological phenomena, are only quantitive, and are never also qualitative. The disturbance, injury or irritation, may cause, he thought, a defect, a weakening, or an increase of a normal function; but they never can, for example, change the character of the function, say of a muscle, to that of a nerve or of a gland.

He considered functional irritability as mainly within the special province of the physiologists, who have chiefly studied it; but he thought of nutritive irritability as more peculiarly a part of the pathologist's study; and in it he held that there is involved an increased intake, into the tissue elements, of growth-materials; and this he thought the most important beginning of the processes displayed in pathological anatomy.

But he elsewhere showed that in physiological irritation there is also a similar increase of the intake of materials.

From this standpoint he viewed hypertrophy and hyper-

plasia, but his illustrations were taken chiefly from physiological data.

From a similar point of view, he studied and explained atrophy and aplasia, and connected them, through impaired nutrition, with the regressive processes, necrobiosis and necrosis, and the so-called degenerations. In so doing, he carefully retained for the atrophies the possibility of a reversion to a norm of the tissue elements which had not suffered any form of necrosis or of a well-marked degeneration.

He explained the normal nutrition of the different parts and tissues as also a manifestation of the activities of the irritability of specially endowed organs and of their elements, the cells; and he demanded that the nutrition must persist, and include in the tissues and cells involved the intrinsic faculty to assimilate and retain suitable growth-materials under due conditions of the environment.

He strenuously asserted that tissues without blood-vessels are yet well nourished, grow and develop; said "they nourish themselves," and are not solely nourished by the nearer blood-vessels, however much these may be factors; he also said, "Each little cell sustains itself as a minute plant does, and selects its nutritive materials from its neighbourhood" (*l. c.*, p. 370).

He urged also as an important fact, that in each organism, or in a part of one, increased growth is not a constant effect of increased stimulation or irritation and supply of growth-materials, and that, especially in pathological phenomena, it is found that a due proportion and grade of these is required for such an effect to follow, and that prolonged severe or acute irritation often may bring about adverse and damaging responses.

He did not here, or I think elsewhere, make a clear distinction between stimulation or irritation as a physiological constant and an "injurious irritation," such as involves damage as a consequence; yet he recognised that responsive processes of this order give us some of the phenomena such as are seen in inflammation, of which he gave as examples the changes seen in the epithelial cells in some renal inflammations; and

he conceived of these as hypertrophies due to irritant actions which had induced an undue increase of the intake of growth-materials into the cells; but so wanting in proportion that the resulting product was not permanent or functionally competent. Such examples can, he taught, be seen in cloudy swellings, in many early inflammations; and he granted the difficulty of confidently identifying them with, or separating them from, true simple hypertrophies.

As he had insisted in regard to non-vascular tissues of higher animals, so he did in respect of non-nervous ones, especially the articular cartilages; and he held with Redfern that they can be inflamed, and are so, in a close relation with the irritation, perhaps experimentally induced; and then they also evince some increased intake of growth-materials in the irritated cell. Expanding this argument to nerve- and vessel-supplied tissues, such as skin, he pointed out that the inflammation responses are limited in area by the irritation of the tissue elements, not by the distribution of the nerves, nor indeed of the vessels; and evidence of this truth is, he said, afforded in observations on epidermis where it is supplied with nerves, but not with vessels.

He referred the observed swelling in these cases to hypertrophy of the cells and tissues, not to their proliferation, for this latter response would not, in his view, be hypertrophy proper.

He made a marked distinction between this teaching, and the common one associated with the saying, "*Ubi stimulus ibi affluxus*," which assumes that the afflux is all or chiefly vascular. He disputed the common doctrine of inflammatory exudation, and adopted the term "parenchymatous inflammation" to signify the changes in the cells and tissues set up, he thought, by an irritation of a particular and exceptional form. He gave a detailed account of such a parenchymatous inflammation in the cornea, granted that it approaches very near to a degeneration, but considered it not so in fact, for it is recoverable by resolution; yet he held this as a good example of an inflammation of this type, and as the highest degree of a nutritive irritation, as manifested in the response.

which is throughout only a cellular and tissue series of changes. He found parenchymatous inflammation, in his sense of the term, very widely spread, seen indeed in all the infective forms.

He dealt with the manifestations of irritation of the formative faculties, often attending and coexisting with those of the nutritive faculties; and it is noteworthy that, although he dealt here with responses to irritation, both physiological and pathological, and so included inflammatory changes, he took an example to begin with from new formations, to wit, from a melanotic new growth of the parotid gland, as if it served to illustrate either equally well. He drew attention in this connection to the division and multiplication of the nuclei, and compared these with the cell-proliferations he believed to be found in leucocytes, in pus corpuscles, and in many normal tissues, new growths, and inflammatory responses. He traced similar nuclear proliferations in muscles, in connection with their initial growth; in repair of injuries, in inflammations; and in new growths; and he followed Goodsir in thinking of the nucleus as the essential centre in relation to cell-proliferation. He in this way approached new cell-formation, and held that the rule is that, after the division of the nucleus, the cell does the same, and so its proliferation results, as the regular mode of reproduction of organic elements; which may be variously related to each other, and may further increase in number or not.

He derived examples indifferently from normal, young, or from irritated cartilage, or from plants, and did not distinguish the irritation here implied, as physiological and reparative, or pathological and damaging, direct or indirect, in its effects. He dealt with epidermis and with connective tissues in these aspects; and although the latter is a more complex structure and has been much misunderstood, he held, by a too great preponderance being given to the intercellular substance in it, with a relative neglect of its cellular components, yet is the significance of the connective set forth as great as, and as instructive as is that of the epidermis or the epithelium; and especially is the cellular proliferation in

it well seen in new growths, even better in them than in inflammation, as the process is not so rapid.

He traced these cell-proliferations in cartilage, and connected them with allied changes in plants, and in connective tissues, so as to formulate a law of continuous development in all organisms. He called all these cell-proliferations growths, and imputed them primarily to the initial fertilisation in which a persisting growth-stimulation or irritation is set up, and persists in adult parts and organisms; without an attempt being here made to distinguish the normal stimulant, irritant, or irritation so produced from any extrinsic or abnormal forms of irritant actions, or their consequences. So that he connected the phenomena of cell-enlargement and of later proliferation by division, seen near a persisting mechanical or other irritant in action, both the nutritive irritations and the formative ones, with the manifestations of the initial normal irritant actions or faculties, without any marked distinctions between them.

He discussed leucocytic emigrations and the fates of such escaped cells, and the various cells seen in inflammatory exudations, and also the products of proliferative processes in regenerating tissues; and held it proven that the formula, "Omnis cellula e cellulâ," is not in any way weakened, but is rather supported, by all the ascertained facts of this order; and the statement still holds, he urged, that new cells are only produced from the substance of existing cells.

He explicitly declared that he had never taught or implied that all new cell-formation began in the connective tissue, or that from this source all new elements were derived; rather he has always studied cell and nucleus new proliferations as occurring also in epithelium, in muscle, and in other living tissues; and in no case has he ever run counter to any real progress in connection with leucocytic emigrations, and the fates which await them: in this respect he considered he had been misunderstood.

He strongly reaffirmed the doctrine that the production of all new formations begins always in the formative or plastic activities of existing cellular elements; and this is

said without regard here to the diverse kinds of cells in the higher animals or plants. He was much concerned to deny that any extra-cellular materials can begin a new cell; but he admitted that within a cell certain substances may be present as the carriers of the formative irritation, *i.e.* of the irritants.

He held that we as biologists must affirm the truth that it is a vital faculty for each formed element to reproduce new elements, and also that such a vital activity persists even when external irritant actions are involved in the succession of changes, and are perhaps essential to their occurrence.

He carefully showed that vascular changes, as such, do not themselves determine these formative irritations, and reactions to them, while irritations of the cells and tissues can do so in vascular and in non-vascular tissues, although he granted freely that vascular changes in excess or defect are factors of some, importance in inflammations and in the irritations by which they are set up.

In like manner he followed the effects of variations of the innervation of parts and tissues; and he showed that they may also be factors often in the production of inflammation, but are not constant in it; and in this way we cannot, he held, explain the irritations of the elements, *i.e.* the cells, of an inflamed and responding tissue.

He urged that the fact remains, that the autonomy of the elements of the tissues, *i.e.* of the cells, persists as a constant in all the responses to irritant actions, in pathological as well as in normal growths and nutritions; so that we find and can experimentally induce such responses in nerveless tissues and in paralysed parts by the employment of directly acting irritants.

It is to me noteworthy that he granted that there is demanded always a particular irritant, extrinsic or intrinsic in origin, in order to produce a characteristic excitement or irritation of the tissue element or cell. In this way he traced a series of gradations between the responses to pathological disturbances or irritations and those to physiological ones, that is, between inflammations, tumours and simple repairs. He explained this position by a reference to his three forms

of irritative actions, functional, nutritive and formative, as above given.

He dealt thus especially with the inflammatory irritations, and said the responses are not simple, for the process is a complex one. In it he held that all possible forms of irritation are present, and in the same inflammatory focus we find the responses are functional, nutritive and formative, as may be seen in an inflamed muscle, in which often pus is produced, as he taught, by a true formative reaction. In inflammation of the same tissue, muscle, he found also simultaneously progressive and regressive phenomena due to changes of, and defects in, the nutritive faculties; I think he meant constantly.

Of the process as a whole, he says, "The inflammation as such then demands neither nerves nor vessels, neither pain nor exudation; it can exist as a simple nutritive or formative process, only distinguished from other similar ones by its characters of acuteness and of danger" (*l.c.*, p. 339); so that he included in it "damage."

After an investigation of many varieties of regressive phenomena, including both degenerations and necroses, he again took up inflammation, especially because it is so often the cause of such regressions.

He considered that the inflammation idea has been much changed since its beginning, by and in observation and experience; and although it has been even in recent times considered ontologically as an entity, and in its nature and essence always and everywhere a similar process, he held confidently that it is not so, but that it is rather a succession of particular forms of different processes (*l.c.*, p. 472).

It is, however, to me singular that he did not give an explanation here of the actual common amid the variable in this succession of different processes, which by implication he obviously accepted as manifesting inflammation.

He referred here, in connection with the process of inflammation, to Galen, and the traditional four signs, "calor, rubor, tumor, dolor," noticed the original dominance of heat, then of redness, and the resulting, almost exclusive pre-

dominance of the vascular phenomena, which, however, he excluded as not constant, as he also did heat, swelling and pain. He pointed out here that we cannot escape, even if we accept in the main the views of Andral and Broussais, from the idea of the irritation, and the irritant, and says (*l.c.*, p. 474), "We cannot think of an inflammation without an inflammatory irritation, and it remains to ask how can one best understand or mentally present such an irritant."

This passage almost says that all responses to irritation are inflammations; but this is not really his meaning, for some responses to irritation are, he held, efficient and normal, in his sense of the word irritation; and not all pathological responses to irritation are, he seemed to hold, inflammation, unless the irritation had been inflammatory.

In no case did he grant that any one of the four classical signs of inflammation is constant in it, and characteristic of it, even in the higher animals, nor did he grant that their concurrence is so, or that the idea of inflammation would be satisfied if we were to add the fifth sign, "functio laesa"; and obviously the concurrence of all of them was out of consideration for inflammation in a general pathology, as he studied it, *i.e.* as a part of general biology.

Herein, if as yet by implication mainly, he retained cell-proliferation in inflammation, and this may perhaps involve swelling, but, if so, not in the sense of an exudation.

He adopted the view that the irritation by which an inflammation is set up always involved his threefold disturbance, functional, nutritive, and formative, and that "functio laesa" is a fifth sign, but he did not say a characteristic one. In any case it is clear that he considered a particular irritation to be an adequate cause of a local cell-proliferation in inflammation, although he did not say that it misdirected the cell-multiplication and development, or that it is peculiar to inflammation, or is characteristic of it.

In all the cases he found that the irritation must determine a change in the living normal cell-substance, that if it be slight it may increase the function, if very great may destroy it, and, when it is of an intermediate grade, it involves also

both nutritive and formative changes in the cell-substance; and all these consequences are, he held, certain results of experience.

So thought of, the normal or physiological stimulation, or irritation, which he here included, is only in degree different from the abnormal or particular irritation which, he held, initiated inflammation, and not in kind; and he did not here assert, or seem to think of, a specific irritation as a cause of, or essential factor in, the process of inflammation which may follow. He said (*l.c.*, p. 475), "If we desire to speak of an inflammatory irritant, we can at present think only of that which, derived it may be from the environment or from the same organism, perhaps from the blood-vessels or the nerves, sets up in any part a state of irritation by changing in the elements of the part their mixture or composition, and so modifying their relations to the neighbouring parts, as to enable them to draw, either from the blood-vessels or the tissues, a larger quantity of materials into themselves, and to appropriate them according to the circumstances. Each form of inflammation we know of can in this way find its natural explanation. Each, it is seen, begins as an inflammation at the moment when the increased intake of the materials in the tissue commences, and the consequent interchanges of such materials are introduced."

I do not find that he gives any other or more satisfactory explanation of the meaning he attaches to "inflammatory irritation" than this, which is not altogether adequate.

He pointed out that, some apparent analogies notwithstanding, these conceptions do not demand blood-vessels, hyperæmia or other vascular phenomena, as has already been said in connection with non-vascular tissues. Yet, he was careful to note that in parts and tissues of diverse structures and faculties, the inflammatory responses differ; and that in these cases the vascular tissues are important, and so also are other intrinsic qualities of the tissues, as may be seen in inflammations of mucous and serous membranes, and of other structures and organs; apart from the degree of

severity, and other characters of the irritant, to which, however, he gave but little relative attention.

Inflammatory exudation as such, and as commonly accepted, he criticised, and explained its variations by taking fully into account the circulatory phenomena, the cellular and the functional attributes of the parts. In this way he founded his subdivision of inflammations into the parenchymatous and the exudative; but he did not make it a constant or general one, or deny that both may occur together, as in a mucous membrane.

He recalled and discussed the common division of inflammations into the purulent and the adhesive forms, as founded upon Hunter's researches; and pointed out that we must first consider in what way and degree the affected tissue is changed and tends to degenerate, and in what way liquid exudations may tend to free it from injurious influences or materials tending to produce degeneration.

Here he evidently thought of inflammation as a process which could be sometimes salutary to the organism in some ways.

He thought every parenchymatous inflammation tended to change the histological and functional characters of the part affected; and every exudative inflammation tended to free the part from something injurious in it, and more rarely led to any durable degeneration than did a parenchymatous inflammation. But he did not deny the constancy of the damage done in either form.

On these grounds, he conceived, were founded the old-established lines of treatment which tended to favour discharges and fluxes.

He separated the parenchymatous and the exudative inflammations further, and said they differ "in nature"; he would call the former "inflammatory degeneration," and the latter "inflammatory secretion"; yet he granted that both forms are caused by an irritation, and that neither can occur without this; and he said (p. 481) "that the same irritation excites here a degeneration, there an exudation"; in short, in both forms he found associated the common signs of inflam-

mation, while yet he did not connect the consequences with the causes, as measures one of the other, or dwell upon the diverse kinds and degrees, or specific characters of the irritants. in relation to the varieties of the inflammation, or set forth what in his view are the common or constant signs of inflammation.

However, he saw clearly the clinical diversities of these two forms of inflammation, and the real relations of both to the intrinsic, normal faculties of the organism ; but he thought the conclusions so reached were often anatomically false. In this path, he held, we are often misled, and so are induced to seek for "a single anatomical definition, and so far each attempt in this direction has been a failure" (*l.c.*, p. 481).

He entered somewhat in detail into a study of the formative irritations in connection with new formations, in the sense of tumours, with which, as much as with inflammatory responses, they are, he held, connected. So that he retained his wide conception of irritation, not only in relation to normal processes, and to inflammations, but also to the beginning and progress of new growths, considered as somewhat distinct from inflammations.

He started with the accepted law of a continuous development of the cellular structural elements in all organisms, and pursued it in a study of tubercle, and of some of the products of enteric fever irritations ; and he found in each and all of them, cell-proliferations at the beginning of, and as a necessary part of the continuing process ; and through these investigations he passed on to a study of the connective, the epithelial, the lymphatic tissues, and their connections, including leucocytes, to the beginning of all new growths or tumours.

He developed the idea of the general presence of the connective in all organs, in some equivalent form ; of its cellular construction, and of the great importance of this structure in connection with the beginning of a new growth, whatever may also be the importance of other cellular tissues.

Much of his argument here is directed to show the inadequacy in this connection of the older views as to the extra-cellular elements, such as the cytoblastema, and also of

the exudation, and the greater significance than had previously been granted of the connective tissue cells and their nearer associates. In this way he traced the beginning of tumours in such organs as liver, brain, or cord, mainly to the connective tissue and its adjuncts.

He called attention here to the law, of which Müller laid the foundations, that cell-production and development in a fertilised ovum, and in pathological processes, is essentially the same, and he pointed out that this implies the pre-existence of cells with their faculties.

He studied the question of the fates of emigrated leucocytes in frogs or in man, in connection with the beginning of new growths, whether tumours or not; and he taught that it does not materially change the problem; because the emigrated leucocytes, whether or no they are derived from the connective tissues, or from the lymph-glands, or elsewhere, are in any case newly proliferated somewhere, if not perhaps always in the place where they are accumulated. He accepted, at least provisionally, the view that these somewhere proliferated cells can further multiply and develop, and he thought of them as having various origins, yet always as derived from cells which were closely related to the connective tissues.

He studied the modes by which cells proliferate, and he put these in two divisions—by fission, and by endogenous new formation; he found examples of the former in epithelium and in cartilage, and in other connective tissues, normal and abnormal, often under the influence of irritation, which is frequently mechanical; and of the latter, *i.e.* the endogenous multiplication, of which he granted we know less certainly the details, he found examples in some normal and abnormal tissues, *e.g.* in the thyroid, in tumours, as in carcinomata, and in many inflammation products, *e.g.* in some forms of pericarditis. He noticed also other and less certain modes of cell-multiplication, in which endogenous and fissiparous changes seem to be concurrent or successive, and these also in diverse abnormal states, carcinomatous or tuberculous. But he held in all the cases that a pre-existing living cell is demanded.

Even a greater uncertainty, he granted, exists in respect of

the cells within cells, such as mucous or pus cells within an epithelium cell, and these he left open.

In any case, he held, there can be only the two main modes of cell-proliferation, whether physiological or pathological, that is to say, the mode by fission or by endogenous new formation; and this, he contended, is true also of plants; and the fact is, he held, well known to botanists, who think of the proliferation by fission as the usual mode of growth, and the endogenous mode as the reproductive one; but both modes are, he held, met with pathologically in plants.

He studied granulations, but first called attention to the fact that in efficient responses and growths of this order, the result is the production of a new formation from the development of new cells, which have a regular conformity with the tissue from which they sprang. Such a new formation with development has been called hypertrophy, but he would rather speak of it as a hyperplasia, on account of the increase in the number of the tissue elements; and so he held there is in such a case not only a nutritive irritation, but also a formative one. In the granulations, he held that the cells multiply by fission repeatedly, and produce many smaller ones, may even, he taught, thus cease to multiply, yet often may again enlarge and develop into a tissue like that out of which they began, so as to produce a hyperplasia. In this category he placed those new formations which begin, he thought, in emigrated leucocytes or in transposed connective tissue cells.

There often follows, however, he held, a different development of the newly formed small cells, *i.e.* a heterologous development occurs. I do not find that he gives any adequate explanation of the etiology of this heterologous change in the development of the new granulation cells.

Cells may sometimes perhaps enlarge, and yet only the nuclei multiply, or at least chiefly these, as he held is often seen in emigrated leucocytes, and in pus corpuscles. In new growths this phase is also, he thought, common, and the stage of multiple nuclei may be prolonged before a fission of the cell is seen.

In the endogenous new growths, however, heterology is

a more frequent result than in the fissiparous ones, as the endogenously produced new cells are, he taught, apparently indifferent to the influence of the mother-cell substance.

He here seems to have assumed a stage in the tissue elements in which one cannot foresee at the beginning whether the new growth will be benignant or malignant, homologous or heterologous. This stage is, he thought, one of absolute indifference, and he calls it "the granulation stage." It is, he held, not always discernible; but it is then not the less real and necessary as an actual delicate and internal material difference, which he compared somewhat with the essential attributes of the primary formative cells of an embryo.

He gave a careful reconsideration to and a denial of the existence of a generally spread cytoblastema in the organism; and he asserted the existence of a generally diffused proliferative cellular tissue, for example, the connective, for which he demanded "a uniform similar irritant in it everywhere" (*l.c.*, p. 495). He gave, as an example of his views in these regards, bone, in respect of its origin, development, and growth; of its various pathological changes, both in inflammation, and in the various new growths it presents.

He studied in detail in physiological and pathological processes the succession of changes which he called metaplasiæ, and saw in each series proliferations of pre-existing cells, with later modifications, irrespective apparently of the kinds of irritant actions by which they were, as he thought, set up.

He found in the simplest reparative responses, and in the most varied inflammatory ones, and in all the new growths, essentially similar proliferative changes, with modifications or metaplasiæ of the products; but he did not deal with, or seek to explain here, the differences in the latter, by equivalent divergences in the kinds of the irritant actions.

In this connection he explained the production of pus, in all its stages and grades, as associated with granulation tissue; and he said (p. 524): "It begins not out of a blastema or from a particular act, not from a new creation, but it develops itself regularly from generation to generation in a perfectly legitimate mode; and this is just the same whether

its elements were derived from those of the pre-existing ones of the part, or whether they were derived directly from the blood into the tissues at the focus." Here he would seem to have attempted to meet Cohnheim's views, and said (p. 524): "We find in the history of diseased bone a complete series of tissue metaplasiæ before us. The first-produced bone from cartilage or from connective tissue can be changed or metaplased into medulla, into granulation tissue, and at length into almost pure pus."

He concluded that the normal and the pathological processes in bone teach us that a series of permutations and transformations or substitutions occur, which progress in different modes, and yet are always connected together and are continuous, "in accordance with the conditions present in the focus." He held that we have in the whole series only the red medulla as the type of heterologous tissue-formation, inasmuch as it consists of the smallest cells, is comparable with young embryonic tissue states, and with "true granulation tissue in its type"; and he adds (p. 525): "Wherever new formations begin in a massive way, there occurs the growth of a tissue of the type of a granulation, and analogous to a young medullary substance; and no matter how solid and firm the tissue may have been, there always a cell-proliferation can take place, which lays the germ for the growth of the later elements of the structure."

He strongly impressed the doctrine that all neoplasms are substitutions, not exudations; and that all cell-proliferations, such as we see in a simple fission, imply a destruction of the proliferating cell, not in the usual sense of the term, yet truly so.

From the known facts it results, he held, that all new formations are homologous or heterologous. Commonly, he held, it is thought that the product of the growth of a neoplasm is distinctive, if it differs more or less from that tissue out of which it began; and this, he thinks, is a legitimate basis for a structural classification of new growths; and such growths are heterologous, whether or no they are commonly called malignant by pathologists.

Those new growths are, he considered, homologous which resemble in their type the tissues out of which they grew, *e.g.* the myomata, or the fibromata of the uterus. Those products, say, of a catarrhal inflammation, are, he held, heterologous which are in a local excess and disorder, and differ in an important degree from the cells and tissues from which they are derived, *e.g.* in fluor albus. He taught that, in the strict sense of the word, only the heterologous new formations are destructive in their progress, while the homologous ones are not destructive or malignant, however damaging they may be under some conditions. He considered heterologous new formations of all kinds, therefore, as peculiarly malignant or destructive, and he gave as instances extensive and prolonged catarrhal fluxes from mucous membranes with erosions, using the term malignant in a sense not now common.

He dealt with the massive destructions of tissue in ulcerations, and with the formation of cavities, and said the contradiction which seems so apparent between the production of new tissue and its destruction is not real, yet is it very striking.

He recalled the cases in which newly formed cells are separable and mobile, or can be carried in a stream; also the various transformations, normal and abnormal, which cells may pass through as they multiply and develop or degenerate; as in bones, especially in the medulla, which is often nearly liquid, and is sometimes so near akin to pus as to be scarcely distinguishable. He said (p. 529): "Pus is for us a young tissue which gradually and even rapidly multiplies its elements and dissolves the intercellular substance. A single connective tissue cell can produce a dozen corpuscles in a very short time, as pus cells have a very rapid productive faculty. But the result is for the organism useless, the proliferation being luxuriant." The pus formation is, he thought a consuming process in which superfluous parts are produced, which do not induce durable consolidation of mutually beneficent parts and tissues, such as is required for the maintenance of the organism.

He reviewed the history of suppuration in respect of the

sources of the pus corpuscles, whether from the blood or the tissues, *i.e.* the leucocytes or the epithelial or the connective tissue cells; and he held the question still to some extent open as to their production also from some of the tissue elements of muscles, nerves, vessels, or connective.

He returned to the question as to the beginning of suppuration from the exudations, the emigrated leucocytes, as first described by W. Addison and others; and he thought that in any case, where pus is being formed, there, besides leucocytes, we find also evidences of cell-proliferations from the tissue elements of the part, although he granted that Waller and Cohnheim have shown a much greater numerical predominance in the emigrated leucocytes. He gave full credit to Cohnheim for his discovery of the emigration of the leucocytes through the vascular walls as an active process.

He did not here or, so far as I know, elsewhere adequately distinguish emigrated leucocytes or intra-vascular ones from pus cells as we now understand them, perhaps because at that date he had no adequate knowledge of bacteriology or of pyogenic microbes. He maintained, however, that not all the small rounded cells found in an exudation, or in pus, are derived from the emigrated leucocytes or the lymph corpuscles, but that some come from the tissue elements of the part by a cell-proliferation, and yet are pus corpuscles.

He pointed to the erosions which usually, perhaps always, attend suppurations on free surfaces, and the greater destruction in deeper tissues, and held that the pus is not itself a dissolving material, but a transformed or partly liquefied one, and that it is not the completed pus which is the solvent, but that the solution was the outcome of the transformation process by which the pus had been produced.

He traced the formation and development of an epidermal pustule, and saw in it both the leucocytic emigration, and the cell-proliferation from the local tissue elements; and he traced similar processes in mucous membranes, both with and without erosions or ulcerations, yet always with some emigration of leucocytes, and also with some local cell-proliferations. He pointed to the liquid exudations attending

these processes as helping to the escape of the pus, not as its source or fount of origin, as the old idea was. He compared pus corpuscles, mucous corpuscles, and proliferated, often separated or modified or young epithelial and other cells, and he attempted to indicate their distinctions in the exudations.

He said (p. 535): "The elements from which new tissues develop are young forms of, or indifferent formative cells; but they are not truly pus corpuscles"; and again: "The youngest elements which are produced under pathological conditions cannot properly be called epithelial cells, at least not typical ones, but rather they are indifferent formative cells, which can also become mucous or pus corpuscles. Thus pus, mucous, and epithelial cells are pathological equivalent parts, which substitute each other, but cannot functionate one for the other."

He granted that often, but he did not say always, in these cases there are some degenerative or regressive changes in the focus. He dealt with such degenerations as best seen in deeper parts, and particularly in connective tissues and their equivalents.

He traced the succession of changes in the near neighbourhood of a mechanical irritation, saw therein, first, an enlargement of the cellular elements, or hypertrophy, then a proliferation of their nuclei, then of the cells themselves, a hyperplasia. These cells remain small, and but little if at all developed, but are locally accumulated; and therewith there comes some softening of the intercellular masses and infiltration; and the relations of these phenomena to the emigration of leucocytes or to pus formation he left a little doubtful, but he was certain there was always some cell-proliferation.

He held, however, that we see especially well where the epidermis is intact, and at the periphery of the focus of irritation, very little or no change; but in the central parts of the infiltration suppurative changes are patent, and they often end in pointing and bursting; and simultaneously we have presented a granulation tissue, with soft or liquefied intercellular substance, and various numbers of small rounded cell-like bodies, in which evidences of cell-division are not constant,

or not equally so in all parts of the focus; but nearer to the periphery there are seen what he called true pus corpuscles, or cells not distinguishable therefrom. The product gets free, some parts are destroyed, the pus escapes, and an ulcer results.

He insisted that ripe pus is not a solvent of organic tissues, such as bone, as he says surgeons have well shown; and he imputed absorbent or dissolving powers to the young proliferating granulation tissue out of which, or by which, the pus is, he taught, formed.

But he was concerned about the difficulty of connecting the progressive processes, such as are seen in the production of a granulation tissue, with the regressive processes, such as are seen in the softening above mentioned, and he tried to explain it by saying, that a stage occurs in which one cannot with confidence say, in a focus of change, whether the process is one of growth, or of the development of a destructive heteroplasia.

He urged that this kind of development of a heterologous new formation is not limited to the pyogenic forms, but is seen also in every other heteroplastic new growth, or development, *e.g.* in the carcinomata and in the sarcomata, if one observes them widely and in their earlier stages of growth, when the cells are indifferent; although, he said, they can and do (*l.c.*, p. 539) "later differentiate, each in its proper type, in accordance with the peculiarities of the irritation by which they were set up."

This is one of the few instances in which he takes verbal note of the effects of particular kinds of irritant actions; and it is the more interesting to me on account of the comparison he makes between the inflammations, some at least of which are specific and parasitic in their etiology, and the malignant tumours.

He traced a comparison between the ulcerative and other regressive changes in suppurations and in cancers, and continued the study into the growth of tubercle, pointing out how erroneous was the older view as to all of them, but especially the last-named, which saw in the products of degeneration, *e.g.*

caseation, the characteristics of the beginning and progress of the malady.

He called attention to the diverse developments and differentiations of different new formations, in relation to their ages or stages of growth, and durations of life, but without reference to their etiology, or to parasitism, and this both in suppurations and in tumours; and he pointed out that, while some tissue elements disintegrate, others multiply, in other parts of the same focus.

He denied for all new growths or inflammatory products persisting maintenance in middle life, as he calls it, of parts which have a liquid intercellular substance; and he said even in solid growths, as in cancers, some parts die and disintegrate, while yet as a whole the tumour lives and grows, and some of its cells proliferate; though in some new growths, as in some so-called polypi, the whole growth seems permanent and durable.

Most new growths, and inflammation products, even though they begin at a point, do not grow and extend interstitially or directly from it, but rather by development of other new growths of the same type at or near the periphery of the focus, while in the centre of the focus degenerative changes occur, often admixed with some fibrosis.

Thus, many tumours are, he considered, as a whole, complexes of conjoined smaller new growths, more or less grown into one whole, composed of often sub-miliary new growths, which, whether suppurations, tubercles, or cancers, each sprang from either one or a few single cellular elements, so that in all these cases we find the younger growths at the periphery, and the older in the centre, where they are commonly degenerated; and at the periphery the new growth extends, where the conditions are suitable, in a zone which is commonly not visible to the naked eye.

A local infectivity is, he held, thus shown to be present in this zone, or, as he called it, a contagious habit, as if this were an intrinsic faculty, which implies that he thought of the production in the focus of a contagious stuff. Hence arises, he held, the surgical need for wide excisions of

such new growths, and so is given an explanation of the lines along which they spread most easily, *e.g.* by the lymphatics; and the relatively slow spread of malignant growths in cartilage or fascia. He concluded that this spread of infection is mainly by abnormal liquids, in which he was not always certain that cells were conveyed; yet he thought it might be so, though sometimes perhaps otherwise; yet he held that the infectivity of these cases strongly upholds the cellular pathology, and that the local structure and vascular and lymphatic distributions in the part affected, enable one to foresee the lines of spread, apart from any consideration of the particular characters of the local disease.

He reserved an open mind as to some metastases, yet inclined to the view that a frequent mode of spread is by cells in currents, while granting that in some cases the spread is against the current. He granted the possibility of a dissolved or liquid contagious material, but not yet the proof of it; referred to the cases of infection by fragments of tubercle, but was hesitating as to his conclusions; yet he saw that these cases do not show any dissemination of the tubercle by living cells of it. This view was in reference to Villemin's experiments and before Koch's discovery of the tubercle bacillus, and he took no account of a possible parasitism by extrinsic irritants.

He thought the older view of the parasitism of a new formation which is useless to the organism is tenable now. He expanded at the same time the idea of parasitism, so as to derive it from the normal tissue elements, each of which is, he held, in a sense parasitic in the body, and conceived it as possible that a mobile separated connective tissue cell in a new position may there exist and nourish, and act as an entozoon. He held that the idea of parasitism is commonly limited to that which involves some damage to the organism affected.

But he did not limit his conception of it to a single series of new growths, and he included with it all the formative responses to irritation, especially the heteroplastic ones, or such as in their further development do not produce any

results serviceable to the organism; nor, indeed, such as are harmless to it; and he held that every new formation begins with a destruction of tissue elements, and lives as a robber upon the growth-materials of the organism affected; so that in this sense each is a sort of parasite, yet is it not separated from the normal tissue elements, except by the damage done.

He treated of "the form and nature" of pathological new formations, and briefly summarised the history of the classifications of new growths, and criticised them. He pointed to the coarser physical characters of new growths, and their histology, and to their comparison with normal tissues and organs, as useful, but not as adequate data for their classification. He considered "the form and nature" of the new growths in their relations, meaning by the "form" the anatomy of the morbid products, and by their "nature" the qualities or conditions he called malignant and benignant; and he traced these in various papillary growths; but for him "the nature" of a new growth did not at all include its extrinsic etiology, to which, indeed, he gave very little attention.

He studied with care the various papillary and other new growths, in respect of the evidences of carcinoma they may show, mainly as an anatomical question; he did not think that cancer can be distinguished by the characters of the epithelial excessive or disorderly productions in them; and he insisted on their co-operation or conjunction with other and deeper tissue-growths, apparently involving always the fibrous or vascular tissues. He held that, as there are true simple histioid connective tissue-growths of the surface in rounded forms, others as warts and papillomata, so there are cancerous growths, such as cauliflower growths and others, constructed in both forms.

In regard to the relations of "the form and nature" of new growths, he recurred to tubercle, and studied its history in the works of Laennec and Bayle, in connection with the older meaning of the term tubercle, as a small swelling; and also with tuberculous infiltration, in connection with caseation, and the modes of its production.

He criticised adversely and explained the so-called "tubercle corpuscles" seen in caseated masses, said they are all dead, but they sprang from pre-existing living cells or nuclei, and that in such a caseated mass we find products of a degeneration of pus cells, lymph-gland corpuscles, and even of cancer and sarcoma, with the so-called tubercle corpuscles.

Virchow granted that the greater part of the material in a so-called tubercular infiltration is really an inflammation product, and so it is not a simple true tubercle, thought of as a small swelling, in the older sense of the word; one which Robin has shown proofs of in tubercular meningitis, in which it is seen to be constructed of cells, is a true new growth, which springs from connective tissue, grows and invades the nearer tissue in a small "tubercle" or swelling by a cell-proliferation, with modification, the cells of which may be small or large, and may have one or many nuclei, and present all stages of transition from normal connective tissue cells to those which compose the tubercle.

In its development, tubercle, he held, stands nearer to pus formation than to the higher new formations, such as carcinoma or sarcoma, in which the cells and nuclei are larger and more fully developed. At first it, like other new growths, is more or less vascular, but the cells, which are small and not durable, so collect as to compress and even close the smaller of the vessels, not the largest, and in the centre they die, caseate and dry, even, it may be, through the whole focus.

Herein he showed a continuous relation between the beginning and progress of an inflammation, including the formation of pus, and of tubercle, and the most malignant of new growths or tumours; while he maintained some, perhaps important distinction, as in his explanation of the so-called infiltrated tubercle, between the results or products of such a mixture of inflammation with tubercle, and the growth of a simple tubercle; all the changes being, however, in his view characterised by some new cell-proliferations, and all, it would seem, caused by irritations, which were not, however, in his view all quite alike. The larger tubercular masses are,

he held, never simple, but complex, and the true small tubercular nodules are found in their soft vascular peripheries, as is often seen in a brain.

The form and dimensions of a tubercle are, he taught, due to its initial growth by cell-proliferation, with early degeneration and death, of the new cells derived, he thought, from the connective; their arrangement in regard to each other in such a way as to check the further growth of the small initial mass, and in part so as to occlude its smaller vessels and induce the regressive or degenerative products seen in caseation.

This series of events indicated for Virchow what he called "the nature" of tubercle; and this term had apparently in his mind no relation to any extrinsic or specific irritant cause, or to any exact etiology, and is explained, he thought, adequately on anatomical grounds.

Caseation he held to be the regular outcome of tubercular growths, but not the sole one; as it may be replaced by a simple fatty metamorphosis capable of resorption. And it is seen also in the products ot other morbid processes, such as pus, carcinoma, sarcoma, syphilitic gummatous swellings, and certain enlargements met with in enteric fever. It is a product of a degeneration, and in itself cannot always show from what primary morbid change it began, *i.e.* whether from a tubercle, a tumour, or an inflammation. In all cases, the diagnosis must rest upon that of the earlier developments of the new growths of any of the kinds dealt with. Thus, all these pathological new growths begin as cell-proliferations, after some irritations not specifically distinguished, and have this in common; but Virchow did not identify them all as responses to irritation, or as inflammations, on that ground.

A tubercle therefore is, he held, recognisable in respect of its "nature" in part, not by its degenerative results, but by its earlier development out of pre-existing cells; and this conclusion he applied to other new formations, all of which have some conformity with their physiological types, from which we can draw the data for their histological classification; for even the truly heterologous growths have physiological types.

Tubercle, then, rightly studied, is, he taught, seen to originate in cell-elements essentially like those of the lymph glands, and it is therefore a "lymphoid new growth."

Pus he again discussed in its relation to leucocytes, both intravascular and extravascular; and he recognised the typical conformity of the normal and the abnormal cells; but he left it an open question as to what is a leucocyte, what is a pus cell, and what is a lymph cell; and no wonder, seeing that pyogenic microbes were then unknown, and a minute histology of these cells in their different stages and seats was then not adequately studied.

He dealt with epithelial tumours, so-called cancroids, or, as he preferred to call them, epithelial cancers. He denied that they are solely epithelial, pointed to their frequent malignity, local and metastatic; said cancroids are inseparable from true cancers by any anatomical characters, and are like cancers connected by a series of gradations with normal forms of epithelium, as may be seen in the urinary tracts, between normal benignant tissues and apparently homologous or benignant epithelioma, and in the most malignant ones. So that he held it not legitimate to think of carcinoma as specifically heterologous and therefore malignant, or of cancroid as consisting of homologous hyperplastic elements and therefore benignant; and he held that neither form of new growth contained absolutely heterologous elements, and neither of them consisted of quite benignant normal elements; rather, a series of gradations existed in both, and each had real relations with some apparently heterologous epithelia in some parts of the organism.

Notwithstanding the conformities of these new growths in which epithelial elements are contained, the characters of the varieties are such as can be recognised by the distinctions and heterologies they show, when compared with the epithelium or epidermis near, as they arise from or in close connection with the connective of the inner parts of the organ, not solely from the superficies. In this way he conceived that a heteroplastic production of epithelial cell-elements took place in cancroids—a true heterotopie or *error loci.* He contended

against those who say that cancroids all spring from some epithelial elements, that they are not separate in this regard from cancers; as some investigators have maintained that the latter also have an epithelial origin; and to this he replied that a primary carcinoma may begin in a lymph gland or in a bone, or in a brain, or in places or tissues where no epithelial tissues proper are; and although some pathologists deny this, and others have referred the beginning of cancers to the epithelial or to the endothelial components of the lymph vessels, he urged that this view, if accepted, requires but a very small further step to reach the idea of connective tissue cells as the seats of the beginning of cancerous growths. While reserving on these points a confident conclusion, he held fast by the opinion that every cancerous new growth is a primary heteroplasia.

He recognised great difficulties in tracing the objective distinctions of the various forms of these malignant new growths, and he thought sharp distinctions not present, but only gradations. Remembering that in cancers the epithelium-like cells are always in the meshes of the stroma, he concluded that the growth is not a simple one, that it is not a true histioid tissue, but is an organised new growth. He noted that physiologically the significance of the various kinds of these neoplasms differs in correspondence with the abundance of the supply of growth-materials. Thus, pearly growths are nearly dry epithelial swellings, and spread only slowly and locally; the cancroids spread locally slowly, but more and yet slowly, affect the lymph glands; and later still, are sometimes metastatic. In the cancers proper the local spread is more rapid, and the metastasis is earlier and common, while healing is only local or rare or never, as is indeed the rule.

He saw an exception in tubercle, in regard to which it is shown that in all its stages and phases it is infective; but he did not find this fact very important in its relation to the other "infective new growths" in which the early stages of new cell-proliferation are the infective ones; and thus, he thought, is indicated either a transportation of cells or of a

liquid infective stuff; or, though he does not seem to consider it, of an extrinsically derived parasitic irritant.

So also the tumours more closely related to the connective tissues are, he held more benignant when harder, and less freely supplied with liquid growth-materials, *e.g.* the lipomata, the enchondromata and the fibromata—and are more apt to be malignant when softer, or more nearly liquid, as may happen sometimes in all of them, except perhaps the lipomata.

Thus we come through gradations to the sarcomata, which genetically are traceable to connective tissue cells; and in this way he was content to find in a series of histological gradations the "nature" of the kinds of new growth, without much reference to related or corresponding differences in the kinds of irritant actions by which his whole theory says they were initiated, though he did not say directed or misdirected. And he called attention to their local, and later general, infectivity, and to their malignity.

In the whole series of new formations, he said, there can be no doubt that for each a physiological type exists in the affected organism; and the question is left open whether they are in the right place, and whether they produce where they are found materials which are to their immediately neighbouring tissues damaging or contagious, or have any irritating effects.

§ 38. In conformity with all his teaching, Virchow said (*l.c.*, pp. 572-3): "With all the new formations, inflammations, and tumours, it stands as it does with plants. The nerves and the vessels have no direct influence upon their origin or development, and only so far can they have an indirect effect as they help to an afflux of growth-materials, for they are quite unable to determine the beginning of the growth or development, or in any direct way to modify them." And again: "A pathological swelling, or tumour, in a man is produced in the same way as is a swelling on a tree in the cortex, on the surface of a stem or of a leaf, where a pathological irritation has

taken place. An oak-apple which begins in consequence of the puncture of an insect, the tuberous swelling which indicates the place where a twig has been cut off, the overwhelming growth which covers the wound where a branch or stem has been removed, each rests upon an abundant and rapid cell-proliferation, as much as does the growth we see in man in the formation of a tumour or of a growing tissue or part. The pathological irritation works in each case exactly in the same way ; the vegetative relations are exactly the same in type ; and just as little as a tree at its cortex or its leaf can bring forth a special kind of cells in that part which it could not otherwise produce, so little can an animal body."

He insisted, that in such new growths in plants the constituents are those of the parent, often concentrated and in excess, as is seen in the tannin, resin, and gum, and this, he held, pointed to a local excess of the juices due, he thought, to the actions of the irritant. He added (p. 573) : "It requires neither nerves nor vessels in order to initiate such an excessive intake of materials by the cells. This is due to the particular actions of the cells, which attract the neighbouring juices to themselves, and then, by the help of the available materials present, separate, fix, and use them for proliferation" ; and he ended thus (p. 574) : "And thus we at the end again reach the same comparison as that from which we began, that is, between the animal and especially the human body and the plant. The pathologist gains by a knowledge of botanical processes very valuable points of contact for the better comprehension of diseases ; and before all things he will in this way reach a conviction of the truth and value of the cellular theory. There exists an internal unanimity or conformity in the whole series of living phenomena, so that even the very lowest organisms or parts, often serve

us as valuable means for an explanation of the most developed and complex ones. For often in the simple and minute the law is more clearly given to view."

§ 39. The Cellular Pathology is therefore a general pathology, and in it Virchow included inflammation, uses the word, and has the idea, although he does not strictly or narrowly define it.

What is the idea he in fact exhibits, and how far in all organisms does he accept it as extending? He held that ontologically inflammation has not any existence as a uniform thing, in its "*nature*" different from others; but that it is a particular form, or series, of different processes, which he did not describe collectively, or even separately, so as to enable the series to be thereby recognised.

However, he denied separately and collectively the four cardinal signs, as constants, in the series; but said, "We cannot think of an inflammation without an inflammatory irritation" (*l.c.*, p. 474); so that here he gave us one constant, and gave it as a valuable qualifying term, of diagnostic significance. Yet, he did not say, or mean, that all the phenomena induced by an irritation are diagnostic manifestations of an inflammation; for he recognised other responses to it, both normal and abnormal, also due to, or caused by, irritations of some kinds, without any adequate distinction being then made, of the various kinds of the irritation, or of the responses so brought about, such as separated those included in the inflammation from all others.

As he did not accept the concurrence of the four signs as constant in inflammation, nor any one of them, even with the fifth or "functio laesa," as manifesting always the thing he had in his mind, he left the definition somewhat open in these regards.

By implication, and in harmony with his whole explicit

teaching, there remained as a constant manifestation in inflammation, cell-proliferation ; but this he did not limit to inflammation, or hold to be characteristic of it ; although he explicitly connected it with "inflammatory irritation," perhaps a somewhat question-begging expression, as he used it. He employed the term irritation very widely, for the initiation of both normal and abnormal responses, and he saw in all of them changes in the living cell constitution, and, if not very clearly, yet he saw some differences in the kinds or degrees of irritation, without tracing them fully either as to their origins or their consequences.

He divided these changes in the cell-substance and their consequences into three groups, functional, nutritive, and formative, all present in inflammations, though not solely in them, or characteristic of them ; but rather as present also in all living things in normal and in pathological states, and all fundamentally intrinsic. So that he, without hesitation, spoke of various cell-proliferations as due to irritations, as if the irritations had but little influence on the kinds or particular characters of the responses of any order ; and this seems to have led to his placing together in one and the same category many cell-proliferations, which most pathologists now keep very widely separated.

He gave a statement (*l.c.*, p. 475) of what he meant by "inflammatory irritation," and the way in which it brings about the inflammatory responses by actions upon the cells ; he dealt a little with the sources of the irritants, and the modes in which they affect the cells ; but he did not distinguish clearly between these responses, and those seen in a simple repair, or in a new growth, or the other responses of a pathological type, which yet he distinguished from those seen in inflammation ; although

such responses also showed cell-proliferations, and are also often damaging; and he did not distinguish the various responses adequately by their characters, or as related to the irritant actions. He dealt, it is true, with various forms of inflammation, but mainly in relation to the intrinsic faculties of the tissues in which they occur; very little, if at all, in connection with the kinds of irritations which he granted initiate them.

He thought the tendency to which we are led by clinical research to find in inflammation a single anatomical definition is false and misleading, and hence he did not attempt to formulate even a provisional one, useful as it might have been.

He studied carefully neoplasms, and tumours, in connection more especially with the formative reactions to irritation; but he did not separate them from inflammatory ones, nor indeed from the reparative ones; but he put them all together in connection with the law of continuous development of cells in all organisms. He included tubercles with neoplasms, as being also due to cell-proliferations, and so as in the same category with tumours; also inflammatory new formations, and malignant tumours such as cancers, were thus connected in all their manifestations by cell-proliferations, and in their initial causes by irritations, without adequately distinguishing the kinds of these latter.

Granulation tissue was for him largely, not solely, an inflammatory response, and less markedly a reparative one than now is taught; but in any case it was always a cell-proliferation with a beneficent development.

He studied fissile and endogenously produced new formations, in their relations to homologous and heterologous responses, very much as a pathological anatomist, in regard to the tissues and cells out of which they spring,

but very little as an etiologist, or in connection with the kinds of irritant actions producing them; and so he connected normal and abnormal results very largely on anatomical grounds, and he claimed for connective tissue very great proliferative and regenerative faculties, with, however, only one common and uniform irritant, and without clearly demanding any special kind of it for particular kinds of new growths; but for many, perhaps all, of the so-called malignant and infective new growths, he required that the irritant actions should be "*pathological*"; and similarly it is significant that for inflammation he demanded an "*inflammatory irritation.*"

Thus, he in fact recognised three kinds of irritation: (*a*) that common to every organism, and each part of it, especially well seen in connective tissue and in epithelium, which is simple, uniform and invariable, and appears to resemble the stimulation of many physiologists; (*b*) that which he calls "*inflammatory irritation*," characterised mainly by the responses seen in inflammation, which is a casual and not a constantly present series of changes, and is not uniform in its kind; but he does not adequately describe its varieties or its nature; and (*c*) that which he calls "*pathological irritation*," which is followed and characterised by new growths, either malignant ones, or their nearer allies; is also casual in its incidence, not uniform in its kinds; and may perhaps sometimes have been a factor in the production of some of the non-malignant new growths; and of this pathological irritation also he gives no account as to its origin or nature.

In his *Inflammation idea*, then, "*inflammatory irritation*" (*b*) was a constant, even if (*a*), the normal and undifferentiated irritation or stimulation, be included in it; but it is only an occasional event in a normal organism; and also cell-proliferation he held to be a constant mani-

festation of it—only, it was not taught as specifically or etiologically related to the "*inflammatory irritation*," or as directed or misdirected by it.

Thus, although these two were for him constants in all *Inflammations*, and in all organisms, yet were they not separately, or together, its characteristics, or diagnostic indications, because they also in some forms concur in repair proper, and in some tumour productions, even in the most malignant of them. With this proviso, however explicitly avowed, that in repair the irritation is simple, uniform and invariable in all parts, in tumour formation it is "pathological," and in *Inflammation* it is "inflammatory," he connected *Repair*, *Inflammation*, and new growth in one large category.

As these distinctions of the irritations are very indefinite, and even rather question-begging, they do not altogether satisfy. If Virchow had ignored the distinctions here so imperfectly given or implied, between "inflammatory irritation" and "pathological irritation," the cell-proliferations consequent thereon, as he traced them, would not have served to distinguish the processes of tumour formation from those of inflammation production; nor would any other of the observed phenomena have so served; and we should have had thus but one greater response to these irritations, of the formative or progressive cell-proliferative type, which would have included both *Inflammation* and malignant tumour productions, but not those of a *Repair* proper, in which the irritation is asserted to be simple and uniform.

Both of these processes of response to peculiar irritations are pathological; and in each he found as constants, also, regressive or damaging phenomena, concurrently with progressive ones. So that, in *Inflammation*, and in malignant tumour formation, he had in the same general idea,

which included abnormal irritations of some kinds, some abnormal cell-proliferations constantly, and some regressive phenomena tending to degeneration and necrosis ; and he had thus three constants in the greater group, which contained *Inflammations*, and malignant tumour production.

These three constants were, abnormal irritation, abnormal proliferation, and some regressive phenomena. In this group he included tubercle, then not known to be of parasitic etiology ; and, were it accepted that the malignant tumours had a like etiology, these also would in his view, so far as any observed phenomena went, or were spoken of or known to Virchow, be included in an intelligible *Inflammation idea* recognisable by the three constants above mentioned.

This, his *Inflammation idea*, could be manifested in all organisms, and would be an important part of a general pathology and of general biology. At pages 524 and 525 he traced, from the normal to the abnormal, cell-proliferations with modifications in accordance with the conditions present in the focus ; therefore he included the irritations as factors in the responses, and he pointed then to hyperplasia, to cell-multiplications, and to heteroplasia, as phenomena met with often, but especially in *Inflammations* and in tumour formations, which thus were brought very near together. At page 529 he gave his ideas, in this connection, of pus formation and multiplication, and said it is luxuriant, not serviceable to the organism, but is produced by a cell-proliferation, as, indeed, is all new formation of tissue or tumour ; but he did not refer here to the kinds of irritant actions, or their relations to the results spoken of ; nor did he adequately explain the conjunction of luxuriant growth with regressive changes, or correctly trace the production of pus. At page 535, *l.c.*, he separated young indifferent formative cells from pus cells not yet

tissue cells proper, though they, he thought, may become either; and at p. 539 he noted that he thought small, numerous, indifferent cells are similarly produced in early stages of the new formation of carcinomata and sarcomata, just as in pus formation, each in its proper type, in accordance with the peculiarities of the irritation by which they were initiated. So that in these passages he brings very closely together the new formations in the *Inflammations* and in the tumours, so as to make a real separation of them very difficult, except by the help of peculiarities in the irritation, which he grants in general terms, but does not trace out.

His study of central degeneration, of caseation, of necrosis, in tubercle, of peripheral new cell-proliferations, of local and general infectivity in *Inflammations*, and in tumours, tends to closely connect all these responses to abnormal irritations into one group, and to justify the view, which I now take, that his *Inflammation idea* really included all.

See, in the general conclusion, his views quoted from pages 572, 573, and 574, which show that, while he in the cellular pathology included all organisms, and saw in the study of plants, both normal and abnormal, advantages for the student of human pathology, he studied in plants morbid processes going on, which are related closely to their normal structures and faculties of life, and are very closely analogous to processes met with familiarly in man, such as *Repair*, *Inflammation*, and tumour formation; and in some degree, he saw in these two latter close relations with peculiar irritations not quite similar in kind to those which accompany normal life and repair.

He in all this saw in *Inflammation* a series of changes present in all organisms, a series important in general pathology, and he connected it with many new formations

or tumours, more nearly than with *Repair*; and, in some not very well or explicitly stated terms, each with its own peculiar kinds of irritation. Had he defined, if only provisionally, his *Inflammation idea* in all organisms, he would, I think, have included in it (1) the peculiar irritations of cell-substance, (2) the cell-proliferative or progressive responses thereto which are not beneficent to or durable for the organism affected, and (3) the various regressive, degenerative, or necrotic effects or sequences, and all three as constants; but not perhaps separately, or collectively, adequate to a full description of the process or an explanation of its nature; yet so nearly so as to serve practically as a sufficient diagnostic, even in the cases in which the irritation was cryptic.

§ 39. I will next briefly notice the paper by Waldenburg in Virchow's *Archiv* (1863), in which he studied the question of *Inflammation* or its equivalent in plants and in animals, after an experimental research, as well as after a study of past records; and he concluded thus: "Is therefore inflammation possible in plants? Frankly, if we attach value, in the definition of inflammation, only to the consequences of the irritant actions, seen in the disturbances of the tissues and in the inflammatory swelling, and this independently of blood-vessels and nerves, then must we attribute to plants not less than to animals the liability and the faculty to suffer inflammation." As he strongly held, and gave his reasons at length, that blood-vessels and nerves are not essential to inflammation in the higher animals even, and that the process is met with in tissues from which these are absent, he came to the conclusion, that the constant and essential factor in inflammation is not in the vascular or nervous phenomena, but in the cellular; and hence it is met with in plants as well as in animals; even although in the vascular parts of higher

animals the nervous and vascular changes are so obvious as to predominate in them. His final position thus led him to refuse to accept any definition of *Inflammation*, the terms of which demand the exclusion of plants.

To this I would add, that the definitions which demand vessels and nerves, also exclude a large group of non-vascular lower animals ; and these have already, I think on sufficient grounds, been shown to demand inclusion with the other organisms that suffer *Inflammation*.

Waldenburg therefore supported the contention that *Inflammation*, or its equivalent, is met with in all organisms. He fully accepted Virchow's general doctrine, and was even led by it, possibly, into some mistakes ; but, duly and fairly judged, and having regard to the knowledge of the day at which he wrote, his services to general pathology were very considerable. True, his studies did not include the lowest animal organisms, and this fact has been noted by Metchnikoff as an objection to his conclusions ; but his whole doctrine having been founded upon the cell as the elementary organism, was sufficiently comprehensive to include all organisms ; and he did not, as did his critic on this point, exclude any.

§ 40. Take next Paget, whose pathological views were not specially those of a botanist, or of a comparative zoologist, and who was not, in the sense that Waldenburg was, a disciple of Virchow, although familiar with his teaching ; but who studied pathology on a very broad biological basis, with a singularly open mind, and with as much caution and modesty as clearness and precision, from the advantageous standpoints of clinical experience and of pathological anatomy ; and who was thus led to conceive of the position of *Inflammation* in general pathology as not limited to some organisms only, but as including all plants and all animals.

From personal conversations with him, many years since, I have little doubt that the beginnings at least of his ideas on this subject were laid before the publication of the Cellular Pathology by Virchow, and were perhaps in part due to his early love of botanical pursuits; but his later developments and teaching were in general harmony with Virchow's doctrines, and he remained to the end of his great career steadfast in his convictions on these questions.

In his *Lectures on Surgical Pathology* (1870), although ever careful to avoid dogmatism, and to give due weight to all the phenomena most constantly present in the higher animal organisms which then were mainly under his purview, his general conclusions and tentative definitions were always carefully framed so as to be comprehensive of all organisms and to exclude none. See his reference to plant galls (*l.c.*, p. 336), where, while dealing with the influence of the proper tissues of the part, and the altered relations between them and the circulating fluids, as important if not essential factors in the causes of inflammation, he says: "And though with some fear of straining an analogy too far, I believe we may gather illustrations of the same principle from the formation of gall-nuts and other morbid outgrowths from irritated vegetable structures. Here are no flowing, changing nutritive materials, no nerves, no vessels that can be justly compared with blood-vessels; yet local and generally long-continuing injury is followed by a defective maintenance of the injured structures and an excessive production of less perfectly organised new ones, in as near an imitation of inflammation as seems possible in materials and conditions so unlike as the vegetable and the warm-blooded animal structures."

His position on this question is, however, yet more

emphatically pronounced in his *Address on Elemental Pathology* (1880), where, at p. 22, he says: "Here I believe are reasons enough for regarding all those galls and gall-like products of disease generated in plants by insects, as analogous with a large group of the products of inflammation which we study in our own pathology; and the analogy is not the less because neither group can be circumscribed with any exact definition." How close he considered this analogy to be is shown in some of his expressions, as when he speaks of galls as "inflammatory hypertrophies or hyperplasiæ"; and again, "But the likenesses between inflammation in plants and in animals are best shown in their visible structural changes." Again, "Of course, in speaking of inflammation in plants we must be nearly limited to the essential parts of the process"; again, after remarking that heat, redness, pain, swelling, and disturbed function are not "of the essence of inflammation even in ourselves," he goes on to say, "For the elemental pathology of inflammation, as for that of decay and repair of injuries, we must study the altered relations between the elemental formed parts and the varying formless materials about them," indicating thus, I think, with sufficient clearness, the cell as the seat and subject of irritation and the responding thing.

Again, after an appreciative reference to Waldenburg, he says, in speaking of galls and other cecidia with deformations of parts, "all produced by the irritant secretions of insects, and all such as may justly be ascribed to processes of inflammation." Again, speaking of these varied morbid structural changes, he says, "I think we may regard the whole of these as being such as in our pathology we should call inflammatory hypertrophies or hyperplasiæ"; and he goes on, "There is, as in the products of our inflammations, a general likeness among

these new structures, whatever be the part of the plant from which they are derived," adding in this connection, "All these morbid growths have their origin in what may justly be called irritation of the part on which they grow."

To be at once fair and accurate, one must not here read into Paget's words, and his use of the term inflammation, as applied to plants, more than he really intended, and this was perhaps only that in plants we meet with an equivalent of typical inflammation, or at least a strictly analogous process ; and he in all likelihood employed the word inflammation in regard to them as the best available one by which he could express his idea, without the use of a more cumbrous and lengthy phrase or sentence.

In every case, then, Paget taught that *Inflammation*, or its equivalent, was met with in plants as well as in the highest animals ; and although he did not pursue the observed analogies in the lowest animals, his survey, resting as it did finally upon the cell, included them, and so his conclusions were such as comprehended all living organisms.

He, like Virchow, recognised the great advantages and the strictly logical propriety, in the study of complex processes, of pursuing them, not only in their most complex manifestations, but also in their simplest, and of connecting them all in one field of comparison. He pointed out that in plants we have simpler manifestations of the phenomena of *Inflammation*, thought of as responses to irritant actions ; he indicated the analogies of these simpler phenomena with the more complex ones, which, as seen in the higher animals, with their greater complexity of structure and function and increased interdependence of parts, are more difficult, or seemingly often even impossible, to unravel in any other way than by the

adoption of the comparative method in general pathology not less than in physiology.

Thus, he claimed and exercised the right to consider *Inflammation* as a process to be studied in all organisms, and so as a part of general biology. He carefully avoided the error into which so many pathologists have fallen, of pursuing the study by comparative methods as far only as the results attained conformed to certain preconceived theories or definitions, otherwise reached; and so, while availing themselves of the facts which seemed to give support to these theories, as freely and as illogically rejecting those which conflicted therewith. Rather, he took into account judicially all the facts, of whatever tendency, and reserved for his general theory those only which were constant in all cases; and he placed the less constant ones in their true relative, that is, less important, position in the process, as a whole, in all organisms.

In all this he stands in marked contrast with Metchnikoff and his school, and, alas! with too many other pathologists.

Paget recognised fully in all organisms the universality and the necessity of the faculty of *Repair* of injuries as a constant and a normal one, its relation primarily to the cells and to the proper tissues of the part, and secondarily to the vessels and nerves where such existed; and he saw with equal clearness the relation of and fundamental dependence upon this normal reparative faculty, of the damaging phenomena in the responses to irritant actions as seen in inflammation, whether vessels and nerves were present and operative or not.

Thus he appreciated even more clearly than did Virchow the real connection of *Repair* and *Inflammation*, as one in which, in spite of the dependence of both upon the same living mechanism, the cell, the latter antagonises the

former while it endures; so that *Inflammation* always implies some damage to the organism, is, in short, a disease-process; and thus he avoided Metchnikoff's view, which so many other pathologists have also held, that *Inflammation* itself is a salutary and purposive process.

He was saved, I think, from this too common confusion of thought by the wide comparative view he took, and in some degree by the results of his study of plants, from which chiefly he seems to have derived the correct ideas he held as to the need for a certain persistence of the irritant actions in calling forth the damaging responses indicative of *Inflammation* in all those organisms in which it has been found.

§ 41. Although certainly less explicitly than any of the three names above given, as in some degree supporters of the view that we meet with *Inflammation* or its equivalent in all organisms, I may mention here Burdon-Sanderson, as in some degree implicitly giving to it support.

In his article on "The Process of Inflammation," Holmes' *System of Surgery*, vol. v. (1871), he says: "By the process of inflammation I understand the succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality." It is a characteristic merit of this formula that it is comprehensive enough, so that it neither excludes any lower organisms explicitly nor implicitly, nor any tissues of the higher ones. True, by its terms it does not adequately distinguish between *Repair* and *Inflammation*; but then it is to be borne in mind that it is not given as a complete definition of *Inflammation*; and its merit even in this particular is that it takes cognisance of the truth that the *Inflammation process* is one that demands the continued life of the parts involved in it.

As Burdon-Sanderson in other passages makes it clear enough that he considers that, in the process of *Inflammation*, if not by the process, damage is always done, he in this way does implicitly make a sufficiently clear distinction between the vital responses which effect *Repair*, and those which antagonise or prevent it, and so are necessarily associated with damage.

In effect, his formula excludes from the *Inflammation process* only what have been often called the direct regressive or passive effects of injurious agents; while it does include in it all the so-called progressive consequences of "injurious irritation of tissues," and it grants, if only implicitly, that these, although attended with cell-proliferation, are often still damaging; while it also includes as factors the various vital responses due to vessels and nerves present in the higher animals, even if not constant in all organisms or in all of their parts.

This comprehensiveness of his formula, which goes with a certain want of rigid definition, has, I think, had much to do with its qualified but wide adoption by many systematic pathologists, at least in this country.

True, Burdon-Sanderson in this article does not deal with *Inflammation* explicitly as a part of general pathology, in the sense in which I here use the term, or study it from the standpoint of the comparative pathologist as did Metchnikoff, but directs his attention mainly to the steps of the process and to their inter-relations as seen in man and his nearer allies in the animal kingdom, using when convenient such lower animal organisms as were suitable for the research; and in this way the phenomena which received the greater share of his attention were those vascular and nervous ones which, as a consequence of the highly specialised structure and functions of the organisms chiefly studied, seemed to predominate in the processes

both of *Repair* and of *Inflammation*, in them. Yet, even thus, he did not fail to recognise the truth that the cell was a factor not to be ignored, and although he did not speak or think of it as the essential one, as Virchow did, he attached to it a greater importance in the process of *Inflammation* and of *Repair* than did some other pathologists of that day.

Although he saw in *Inflammation*, as primary and even essential factors of the process in man, a disturbance of nerves and vessels first, and a disturbance or irritation of the living cells as a secondary factor ; yet did he find this latter one so important, that he was able to say (*l.c.*, p. 789) : "In all living tissues the effect of *Inflammation* manifests itself in a modification of the action and properties of individual cells. In cells which form part of permanent structures the protoplasm increases in quantity and becomes more or less contractile. Subsequently it is converted entirely or partly into young cells either by cleavage or by endogenous germination."

Virchow might have written this passage. The conclusions he reached were come to from a study of the higher animal organisms mainly, yet were they such as, while applicable to those organisms, were not expressed in his formula or in any other part of his article, so as to imply that other organisms did not present us with analogous processes, the possible equivalents of the actual typical inflammation he studied and expounded.

For all other organisms, animal or vegetable, multi- or unicellular, he takes up a somewhat neutral position ; at least, he does not explicitly or implicitly exclude any. So far as I am aware, he has not changed this attitude in any of his later writings ; and I venture to rank him, therefore, as one of those pathologists who do not explicitly or implicitly deny that in other organisms than those

which he specially studied a process is or may be met with which is an equivalent in them of typical inflammation in man, even although its manifestations may differ much, and then may correspond to the structures and endowments of the affected organisms.

Further, his whole teaching urges that only vital responses are characteristic of *Inflammation*, that all the passive effects or the primary regressive phenomena are outside it, or only indirectly related to it, and that in the vital responses seen in *Inflammation*, whether these are presented to us by complexes of living cells such as vessels and nerves, or by cells more individually responding, and even when they are seen in progressive phenomena, such as in cell-proliferations in a true *Inflammation*, they are invariably damaging to the organism in which they occur; and thus that they are in a marked antagonism to a true *Repair*; however much the series of changes as met with in nature in concrete cases may overlap or be commingled; so that the regressive and the progressive phenomena often may seem inseparable, especially in the more chronic forms in which the "injurious irritation" endures long; and the conclusion thus seems certain, that in his "*Inflammation idea*" proliferation of living cells or parts of them is a common, if not indeed in his view a constant factor.

§ 42. That out of the writings of many other pathologists of repute, ancient and modern, facts and opinions may be gathered, which also go to support in some degree the idea I here contend for, that *Inflammation* or its equivalent is met with in all organisms, there is no doubt in my mind. But, as enough has been said, I think, to show that it does not stand entirely alone and unsupported, I will defer any further references to other authorities until a more suitable occasion arises for introducing them in the course of this discussion.

Meanwhile, I now venture to say, that all organisms suffer injuries and irritations, and respond to these respectively by *Repair* and by *Inflammation*, or by its equivalent, whatever that equivalent may be; and that in many cases, after *Inflammation* ends, *Recovery* begins and goes on. I anticipate with some confidence that by taking thus into one field of view all living things, in regard to a process which has been in the past mainly studied only in some, the conception as to the true nature of that process may be made more clear, even in that form of it which has been most studied, viz. *typical Inflammation* in man.

That some different line of approach, or method of dealing with the problem, is much to be desired, no one can doubt who has realised the existing diversities and even confusions of view in regard to *typical inflammation*, studied as it has been. In this hope I adopt and contend for the following conclusions: (*a*) that all organisms suffer normal and casual injuries, and *Repair* them; (*b*) that all suffer also "injurious irritations," and respond to them in *Inflammation* in a different and characteristic mode, in and by which damage is done to the responding organism, *Repair* is not effected, but is retarded or prevented, during and in the measure of the "injurious irritation"; and (*c*) that these responses persist in this mode, until at length in many cases the "injurious irritations" and the responses they evoke tend to diminish or cease—usually, if not always, in consequence of changes commencing in the irritant; and *Recovery* then begins, *Repair* dominates, and *Recovery* can then be completed, though often by a compromise which is only more or less efficient.

§ 43. I will now attempt to express the *idea of inflammation* in all organisms as it is here understood, so as to

include what has been spoken of above as its equivalent in the same expression; but in all the various manifestations of it, always maintaining an unbroken and connected series of events between the typical forms and the most divergent of its equivalents.

In making this attempt, the common amid the variable will be sought for, and it will be assumed to have been shown that the more common or constant is the more essential factor in all organisms; but, variability being also a very common character, it will demand and must receive adequate attention.

In accepting the type as derived from man, however, there is not therein included an acceptance of the view that all its most typical manifestations are to be found alike and equally in all organisms or parts thereof, although equivalents of all the essential factors there must be; so that, although in organisms not provided with vessels and nerves it is idle to expect to find obvious phenomena indicative of vascular and nervous actions, normal or disturbed, yet is it required to find in all such organisms, in every case, their equivalents, in a due supply of growth-materials. And, as in organisms which are provided with blood-vessels and nerves we look for and find also, besides the vascular and nervous manifestations, others indicative of cell-proliferations, though then they are often less obvious and dominant than in the organisms not so provided, these are then to be regarded as the equivalents in them of the cellular proliferative responses, so much more obvious and dominant in the non-vascular and non-nervous organisms and tissues, especially as they are seen in plants, and in non-vascular animals.

Thus, in all organisms we have the equivalents of two groups of phenomena in the *inflammatory processes* of response to "injurious irritation"; that is to say, the

vascular, with the supply of growth-materials, and the proliferative changes ; and these are always so closely related to each other that neither ever stands quite alone ; but the two are rather indissolubly connected as parts of one whole process.

This necessary and constant association is seen also in the pure *Repair* processes, in which always there is present a cell-proliferation or its equivalent, and also its necessary supply of growth-materials—that is to say, proliferation, and circulation, or the equivalent of either. But in all organisms, in the lowest as well as in the highest, the former is the more constantly observable phenomenon ; in the highest the latter may very often predominate ; the former, however, more often does so in a pure *Repair* or in a regeneration, in which case it differs from an *Inflammation* in this regard.

As in normal life, in nutrition, growth, repair of waste, and in reproduction of the organism, we must necessarily presuppose a due supply of growth-materials, their assimilation and distribution, in the monad as in man ; and as these are inseparable from each other in health and in disease so long as life endures ; the non-vascular organisms and tissues, not less than the vascular ones, can neither exist nor reparatively respond to injuries nor to "injurious irritations," nor recover afterwards, without such assimilation and distribution of suitable growth-materials ; therefore they are both rightly assumed to be present always, even when they are not all obvious.[1]

I pass over here, as not demanding a separate or equally detailed consideration, that stimulus or generally diffused

[1] Here is perhaps a suitable occasion to repudiate Cohnheim's idea of the constant amid the variable in inflammation ; for it is concerned only with the changes in the supply of growth-materials or of the circulatory apparatus, and it ignores the cell-proliferations which in all organisms are the most important constants we can trace in inflammation.

and similar uniform irritation, as Virchow considered it, which many physiologists assume as necessary in all normal organisms, without myself accepting it, though not quite willing to deny it; but seeing that it is supposed to be uniform in kind, if it be present, and is itself not variable, as are the irritations which induce *Inflammations* and tumour productions, I will here speak of the reparative responses as automatic in their characters, and as intrinsic or not directed by a stimulus, or by any irritant actions.

Thus, although the cell-proliferative responses are in many of such cases relatively more distinct and dominant than are the circulatory ones, the equivalents of these latter are yet also present in all cases, in an adequate amount, both in health and in disease.

So that for all organisms responding to injuries and irritant actions as living things, though in different modes and degrees, according to their structures and endowments, the due supply and distribution of growth-materials for cell-nutrition and proliferations is necessary and constant, so long as life endures. Such a supply is indeed inseparably associated with all cell-proliferation, and the two processes mutually influence each other in modes and degrees which have been much debated, and are not as yet all agreed upon; although the existence of such mutual influence is accepted, I think, universally.

Examples of the close and necessary interdependence of the supply of growth-materials, and of the activity of nutritive growth and of cell-proliferation, have been given in Section II., dealing with plants, and they are as commonly found and as well exhibited in animals.

It has often and truly been said of the lowest organisms, especially of the unicellulars, that they move without muscles, feel without nerves, digest without a stomach,

and so on ; and it is quite as true that in them a circulation takes place without any special circulatory organs or tissues ; and were this not so, they would cease to live, to grow and proliferate, or continue the species ; obviously, therefore, they could neither repair injuries nor suffer inflammations.

The intimate and essential connection between the supply of growth-materials and the life of the cell is therefore constant and necessary for the persistence in life and activity of each of the component cells of all organisms, even the highest, in health and in disease ; so that the presence of cell-proliferation presupposes an equivalent of circulation, in the sense of a supply of growth-materials. The converse of this seems also true, and it may therefore be said that the presence of a circulatory apparatus presupposes the existence and activity of its component cells, with all their faculties.

§ 44. The relations existing in reparative responses, and in the damaging or inflammatory ones, between the intrinsic and the extrinsic factors involved in the processes should also be considered.

In the study of *Inflammation*, very much limited as it has been to the higher animal organisms, the vascular and nervous phenomena have naturally received a large amount of attention, at least proportionate to the relative prominence in them of those phenomena ; with, as one effect, a proportionately reduced attention given to the structural and functional responses presented by the cells and tissues, shown often in abnormal cell-proliferations ; and as another effect, a wide disposition to separate, sometimes too absolutely, the processes of response to a simple injury and to "injurious irritation," *i.e.* of *Repair* and *Inflammation*, as met with in the lowest animal organisms and in plants, from those exhibited in the highest,

and in them chiefly and obviously manifested in connection with nerves and vessels.

These pages will, however, have been written in vain unless I have therein given sufficient reasons for refusing assent to the exclusion of any organism from a liability to injuries, and from a faculty to repair them, as well as to suffer *Inflammation*.

And, if we do include all organisms, it follows that the predominance which has been given to the vascular and nervous phenomena seen only in some must yield its dominant place; and thus only a due share would be given to them and to their equivalents; and then only can the real relations existing between the reparative faculties and the phenomena met with in the damaging responses to irritation be set forth, so as to be duly appreciated.

As a fact, although in point of time the vascular and nervous phenomena rightly claim precedence as having been longest studied, and, largely on this ground, it is conceded that they are the most manifest in and give us the typical forms; yet is it also true that they are either absent altogether or are only represented by certain equivalents, often traced with difficulty, in a very large proportion of living organisms. They are indeed, it is well known, not constant in all organisms; and they are less constant and therefore less essential than are the proliferative responses to injury, and to "injurious irritations," in *Repair* and in *Inflammation*, as manifestations of either order of response, when all organisms are considered.

Thus, in granting, as has been done here, that *Inflammation* or its equivalent, considered as a process sometimes met with in all organisms, must stand in an unbroken series of events connecting the different essential parts of

the process in all organisms with the old and accepted type, it is not thereby granted that such essentials are all to be found in the more obvious nervous and vascular phenomena, which in the higher animals are presented to us, to the apparent exclusion of some of the other phenomena, present both in the highest and in the lowest, to wit, the cell-proliferative ones ; although in all organisms, both higher and lower, the equivalents of all the phenomena are and must be present, in every focus which responds in *Inflammation*.

The apparent absence of some of the cell-proliferative responses in a typical inflammation in vascular organisms and tissues is often, perhaps always, due to some deficiency of observation, or to a too exclusive direction of attention to the more obvious vascular phenomena.

Rather, it is here claimed that the phenomena which are universally met with in all organic beings, and are most obvious in the simpler and lower forms, have a greater value and significance in deciding what should be regarded as constant and essential, than those which, although very obvious in the highest and most complex organisms, are, if not absent, reduced often to an obscure trace in the lowest and more numerous ones ; and the most constant phenomena therefore are the proliferative responses in *Inflammation* in all organisms.

So regarded, the most universal among the responses to a simple injury or to an "injurious irritation" are those which are manifested by cell-proliferations in which the necessary equivalent supply of growth-material, though always present, is not an exclusive, and may not be an obtrusive, phenomenon.

That this conclusion as expressed demands some modification or qualification in considering unicellulars I grant freely ; but I need not here go further than say that in

them the proliferation should be thought of as being of the structural units of the cells. But however important, and even necessary, it is in any statement of the *Inflammation idea* in general pathology, to indicate what its manifestations are, and how it is to be recognised, something more than this is demanded for such a statement to be both satisfactory and intelligible.

So far, the conclusion reached has only dealt with the most constant manifestations seen in the responses to simple and massive injuries and to "injurious irritations," without clearly separating these two from each other; and it has said for both that some proliferations of the structural units of the cells, or of the cells themselves, or of the tissue, are for all organisms the most constant phenomena, in some are even the most obvious; although in the highest they are often so much obscured by the responses due to nerves and vessels as to be then less obvious, and have thus been too much neglected.

Some attempts should therefore here be made to explain the origins of these manifestations, that is, their causes, both intrinsic and extrinsic, the effects, reparative and damaging, the real relations between such effects and their causes, the differences in kind and degree met with in such effects of both orders, reparative and damaging, and the fundamental resemblances also present, in the midst of the differences. In this way I must seek to reach also the causes of the frequent cessation of the process, in healing, recovery, or death, and I shall have to compare and contrast *Repair* and *Inflammation*, to consider what are their purposes, if any, and to deal with *Recovery* after *Inflammation*, and with its conditions.

§ 44*a*. Difficult as it is, I must however attempt to show, for the etiology of *Repair*, that it rests upon the evolved reparative faculties, which I have spoken of as

intrinsic in all organisms and as acting under the conditions of a present defect or injury of some kind, which must not arrest or prevent them; at least this is so as regards casual injuries.

That the effect of or response to a simple non-fatal casual injury is always, in some degree, fitly related to the organism, or its part, is directed and measured by it and by the defect or injury, as are all effects by their causes, so that the result shows always relations of fitness to the organism, and to its defect or injury, and that it may be thought of as to this end purposive, is also to be shown; so that the reparative faculty thus can be traced back in evolution to the law of survival of the fit.

Such a conception does not demand the assumption of a physiological stimulus or of a uniform general irritant, and it may be, I think, better thought of as *automatic.*

§ 44*b*. The etiology of *Inflammation* I must also attempt to show as a much more complex conception; so that it necessarily always includes as factors the same intrinsic evolved reparative faculties constantly present and automatically operative; and with them also always some extrinsic irritant factor or factors, co-operating in the causal actions, always through "injurious irritation," and so misdirecting the intrinsic faculties as to dominate the responses in many respects, and thus to determine largely the varieties of *Inflammation* we meet with in nature. The effects of this more complex etiology are seen in the correspondingly complex responses in which the evolved intrinsic reparative faculties as misdirected, may actually damage the organism, and result in a product which is fitly related to the irritant, the misdirecting agent, and, as in other effects of causes, is measured by it. Such responses do not cancel or expel the irritant, but rather subserve its interest, and always,

although carried out by the intrinsic faculties of repair as misdirected, antagonise repair.

Such a faculty to respond to irritation by doing damage, cannot have been directly evolved by a survival of the fit; and the purpose of the faculty, however derived, cannot be thought of as salutary to the responding organism; but rather it is in effect fitly related to and purposive to the irritant which it benefits; and it cannot be fitly related to the organism which it is harmful to.

So long as both the factors, *i.e.* the extrinsic and intrinsic ones, above mentioned are operative, the results are, as stated above, always damaging to the organism.

§ 44*c*. In this complex series of actions and reactions, the prime mover may rightly be considered to be the evolved intrinsic reparative factor, and the perturbing or interfering force, the extrinsic factor, the irritant, in all *Inflammations* in all organisms.[1]

But, if from any cause the extrinsic irritant factors cease to dominate the response, and so to misdirect it towards a relation of fitness to the irritant, the intrinsic factors, which are never absent, then preponderate, *Recovery* begins, and goes on, and so the process ends in a form of *Repair.*

So set forth, I hope a sufficiently clear distinction is shown between the manifestations of *Repair* and of *Inflammation*, the causes and the effects of each of which

[1] It is interesting here to recall Stricker's views; see his *Allgemeine Pathologie der Infectionskrankheiten*, 1886 p. 112: "The view, on the other hand, that inflammation is a reaction which leads to healing contradicts fundamental ideas. That inflammation leads to healing is comprehensible if the patient does not die, as it lies in the nature of the inflammatory process that it leads to a recovery, if only very slowly often. That inflammation is a reaction which follows irritation needs no proof. But that the inflammation itself is a reaction tending to healing contains an internal contradiction, such as he would make who urged that industrial over-production is a restorative of the normal production."

are shown as related and coequal phenomena; and thus are explained also the resemblances and the differences which they present to us in the responses, whether they are progressive or regressive, or both, whether dependent more on the intrinsic or on the extrinsic factors in the etiology ; and *Recovery* is also thus included in the conception. Some repetition has here been unavoidable, and I trust it is excusable on that ground.

This conclusion, that the process of *Inflammation* is not salutary, or its products fitly related to the responding organism, is in conflict with a now widely accepted pathological teaching, as is also the doctrine that the beginning of recovery often rests upon the normal changes in the irritant.

This idea of *Inflammation* as a casual disease-process in all organisms, and as an important subdivision of general pathology, is in harmony with the provisional definition given at p. 2. of the address "On Some Diseases of Plants," namely, that it "may be considered as a reaction of living cells to irritation" ; but this conclusion, though valid, I think, so far, will demand a reconsideration in which due account must be taken of the varieties of disturbances of the reparative faculties not clearly shown to be "injurious irritations."

My view, then, still is, that *Inflammation* must be regarded as a casualty, a perturbation of repair, in all organisms, and always during such a perturbation, the intrinsic evolved reparative faculties of the particular organism, or the part of it affected, persist and are active, and, although adversely conditioned by the extrinsic irritant actions, are yet always operative in the process, and are often, perhaps always, the agents by the help of which the damage is in part done in and by the process.

Inflammation being in this way thought of, it is both convenient and legitimate to speak of the reparative faculties as exerted in each organism by a mechanism, and to give to this the name of the automatic reparator, which in the last analysis is the cell, but intermediately is often the tissues. I conceive of this faculty of *Repair* of injuries, and of its mechanism, as universal and necessary in all living organisms, as having been really evolved in obedience to the law of survival of the fit, and as always and necessarily beneficent; as being both in thought and in fact separate and distinct from, though related to, its casual perturbation, *Inflammation*, which is constantly damaging; and so cannot, as such, have been directly evolved in obedience to the same law.

Yet, as is herein shown also, these separate and distinct things are necessarily, closely, and mutually related to each other, so that, without the intrinsic reparative evolved faculties, the phenomena manifested in *Inflammation* could not be, any more than they could be without extrinsic irritant actions, or be met with in dead cells or tissues.

Such damaging responses as are seen in *Inflammation* and are constant in it are etiologically more closely related to the extrinsic factor than to the intrinsic one, so that the varieties of *Inflammation* we meet with are mainly dependent upon it for their specific characters, although essentially related to both factors.

SECTION V

THE INFLAMMATION IDEA IN GENERAL PATHOLOGY, STUDIED SO AS TO SHOW ITS SEPARATION FROM REPAIR AND FROM ALLIED PATHOLOGICAL IDEAS, AND TO AFFORD THE BASIS OF A DEFINITION OF IT, THE MUTUAL RELATIONS OF ITS ESSENTIAL FACTORS, ITS GRADES, VARIETIES, AND DISTINCTIONS FROM SUCH OTHER PATHOLOGICAL PHENOMENA AS ARE OFTEN ASSOCIATED WITH IT, BUT ARE SEPARABLE ON ADEQUATE GROUNDS

§ 45. THE mechanism of *Repair* is thought of here as an evolved one, and as resting finally upon the automatic reparator, that is, the cell and the cell-complexes. Physiologically, it is universally necessary in all living organisms, and it is that which, founded on the faculties of nutrition, repair of waste, functional and other, enables an organism to assimilate, grow and multiply, that is, to live.

Through these reparative processes, in which the structural units of the cells proliferate, as well as also the cells, *Repair* takes place of massive injuries of cells, tissues, or organs, both those of normal and of casual origin ; and the step is but a small one from the former to the latter, which, though not constant, are so frequent that their *Repair* is necessary for all organisms.

The mechanism through and by which such *Repair* is effected is, or is contained in, the cell, which is its simplest

expression; so that, although a simple cell can and does, especially as may be seen in unicellular organisms, *Repair* a wound or restore a loss by proliferations of its structural units, it can only do so when its own mechanism as a cell is approximately in a normal or complete condition, that is to say, when it retains in a due proportion its essential elements of nuclear-plasm and cytoplasm; and so far as is now known, neither of these essential constituents of a cell, alone, can *Repair* a massive injury of it, even although it would seem probable that, of the two, the nuclear-plasm is the more important, yet it is not shown that it alone is competent; and it is well known that cytoplasm alone cannot do so, even although a mass of it may actively move about for a while, restore a sort of normal film at an interrupted surface, and even present an outward form not much unlike that of the original cell.[1]

We cannot therefore regard the proliferative attributes of the structural units of a cell, apart from the whole of which they are parts, as indicating that they represent the elementary mechanism of *Repair*.

For this, we must come to the whole living cell itself, the elementary organism, the true "automatic reparator." This is never absent in any organism, and in the most complex compound organisms it is always in them, during a *Repair* of massive normal or casual injuries, the effective agent; and it manifests this faculty in cell-proliferations and developments, demanding only adequate supplies of growth-materials and normal life-conditions, in the responses to normal and to casual injuries, and equally also to "injurious irritant actions."

[1] In this conception of the cell I ignore, without prejudging the question, cells without nuclei or some equivalent thereof, and deal only with cells of which we have objective knowledge. Undifferentiated portions of protoplasm, real though they may be, are not included.

§ 45*a*. Parenthetically, here, in connection with the idea of *Repair* as an evolved necessary constant faculty of all living organisms, and intrinsic in them, it is of interest to recall the fact, to which Paget drew attention, that crystals also *Repair* injuries—at least, they attempt to restore an injured or a defective normal form.

However, accepting this statement without reserve, and even adding thereto, as a related one, that in them also the process of *Repair* is sometimes perturbed, as may be seen when the mother-liquor contains some colloid material, it is felt to be quite as justifiable as it is needful, to accept a great and sufficient break between the non-living crystal and the living cell, and to deal here only with the latter in speaking of *Repair* and of its perturbations.

For me it suffices to say, that although a crystal grows and may partially *Repair* some injuries, and even multiply, it differs from a living organism in that it can begin *de novo* in its mother-liquor, without any previously present crystal of the same kind, and that in a similar way it often multiplies ; while, until abiogenesis is proven, we cannot say as much of a living cell, as to its beginning or its multiplication. The cell lives and dies ; the crystal does neither, in any proper or accepted meaning of the words.

§ 45*b*. Consistently with this view, we find that in different organisms the mechanisms of *Repair* present us with diverse structures and faculties ; and in fact, although in them all the living cell is always a constant, it is so variously arranged, associated and endowed, that we find, as in man, the nervous and vascular cell-complexes very prominent factors in the process of *Repair* ; and in the plant and in non-vascular animals these are so little prominent as even to seem absent, without equivalent, when the search is not very carefully made.

The mechanism of the automatic reparator in all

organisms is then, although it always rests upon the cell, very diverse in structure and faculty; and in the same organisms it is not the same, even in these regards, for all of its parts. Some cells or some cell-complexes called tissues, as in man, are in this regard very highly endowed, as we see in the vascular connective, and in the epithelial tissues, and in vascular plants in the great cambium and its allies. And conversely, in the more complex and highly specialised organisms, some parts or tissues, chiefly those with very special functions, are much less so endowed, or it may be in some cases seem not at all so, as perhaps in ganglion cells, at least in some animals. Notwithstanding this, it remains true that all living cells, not so specially differentiated or not yet quite mature, retain in some degree a reparative faculty, shown in an aptitude to proliferate either their structural units, or themselves, or both.

These considerations justify the conviction, that the faculty of *Repair*, as well as the mechanisms by which it is exerted, has been evolved in accordance with the law of survival of the fit, not only in regard to the repair of waste and of a normal injury, molecular or massive, but also in regard to the *Repair* of a casual injury, if only it be frequent enough to constitute a material danger to the survival of the species.

§ 45*c*. In nature there can, I think, be little doubt that the most frequent of the casual injuries are the traumatic ones; and these are commonly more promptly and efficiently repaired, if the process of *Repair* is not perturbed by other influences capable of producing an "injurious irritation," which, when they occur, are mostly parasitic in origin, and the manifestations of which are the most specific, characteristic, and instructive of the responses seen in *Inflammation*.

It is not here intended to imply that the mechanisms by which to so large an extent in the higher animal organisms casual injuries are repaired, are specially evolved and endowed for this purpose only; and it is only desired to point out that the cells or cell-complexes, the vessels and nerves in such organisms, possess, as one of their intrinsic functions, that of contributing in an important degree to such *Repair*; even such as, in some ways at least, may give to them some superiority in the velocity of their repair-processes over other organisms not so provided.

This may be seen in the frequently greater velocity of these processes in them, and in the more effective modes by which they appear to cancel or efficiently deal with some intrinsic hindrances to *Repair*, such as blood-clots and tissue-débris in wounds, crushes and bruises. In the end, however, it is not clear that in these higher organisms the final outcome of *Repair* is more perfect than it is in the lower ones, even if it be more rapid.

The mechanisms vary in different organisms and in their parts, and the modes of working may differ; but in all cases the result is so efficient that the organism benefits, and the part persists.

§ 45*d*. Although it is true that in the higher vascular and nervous organisms the hindrances to repair, which themselves seem to result from their greater complexity of structures and the closer interdependence of their parts, are more promptly and perhaps more effectively dealt with by solution and absorption, and also by phagocytic processes, as well as in other modes, than they are in the lower organisms, and especially than in plants, in which these passive remnants of the injury are usually only encapsuled; yet is it also true that such

inclusions are, at least in plants, more inert and harmless, so that the cell-proliferations and differentiations which follow in them are still adequate for the required efficient repair.

Here I may note incidentally that in plants it is especially observable, that dead, inert masses of tissue quite normally occur as inclusions—as witness the heart-wood of trees, which may and indeed, I think, does, even in this state, contribute somewhat by its mechanical support and otherwise to the welfare of the whole organism or colony.

Moreover, in the lowest organisms, including some plants, in which a definite circulatory apparatus is not developed so as to rapidly convey moving liquid currents, in which also often cells themselves are carried, a process of *Repair* is represented often by an equivalent only of molecular currents; and we find the cell-proliferations with development, on the lines of the injured organism or its part, as well marked and efficient for the regeneration of lost parts as in the highest vascular organisms. This would seem for them to fully compensate for any relative deficiency of speed in some of the processes of *Repair*, due to their imperfectly developed vascular structures or their equivalents. See the well-known superiority of regenerative attributes among the lowest animals, and in almost all vegetables, shown by the reproduction of lost organs or members, and especially well shown in plants, in the common modes of propagation by cuttings, even when these are of very small sizes, if the cultivation conditions are suitable.

§ 45*e*. In this way considered, the general expression reparative faculty must be held to include that of re-generation of a tissue or an organ, the reproduction of

lost members, and sometimes even of a perfect complex organism, as in the growth of adventitious buds from a callus.

For this reason I will here consider the essential relations of *Repair* and of regeneration. The ultimate mechanism of the automatic reparator is, as has been said, in every case contained essentially in the cell, the elementary organism, when we have under consideration *Repair* in all organisms; and, however important sometimes the nervous and vascular organs may be as parts of it in those organisms in which they are developed, they cannot be essential for all organisms, seeing that many have them not; and on the other hand, as there is no organism in which the living cell is not either the organism itself, or an essential and constant part of it, and of every tissue and organ in it; for the *Repair* of all organisms, the living cell is the one constant in the mechanism, and it is demonstrably present in all cases.

The reparator is, I prefer to hold, automatic in its actions, that is to say, the need for *Repair*, the injury, having arisen, is its sufficient condition precedent; this being present, the reparator operates intrinsically, directly, and necessarily, without demanding an intervening physiological growth-stimulus, or enzyme; and such prompt reaction following automatically and immediately the very slightest injuries, such as those of functional waste, effaces or *Repairs* them without obvious break of structure or of function; and all this necessarily, if nutrition and life persist in the part, also in the cases of a massive injury, normal or casual.

Such an automatic action of the mechanism and faculty of repair obtains both in normal nutrition and in casual massive injury, attended with a breach of continuity and a loss of parts, or, as it is often called, a

defect; but its action is manifested then always in a structural unit, or a cell-proliferation and development, attended with an adequate co-ordinated supply of growth-material—enough and not too much; and the product is then always beneficent to the organism, and yields an approximate restoration of the defect or loss; so that it is efficient, persists, and can functionate more or less perfectly.

In quantity, the product is related to and proportionate to the defect, but in quality it is determined by the intrinsic faculties of the reparator itself, which, as has been said, is not alike in all organisms or parts thereof, except that in all the living cell persists and functionates, and the reparative process ceases, that is, arrests itself, by restoring the defect or injury which conditioned the process.

Here is no included question of a persisting intrinsic or extrinsic stimulus to growth, or of irritant actions of any order. The action by which the massive injury or defect had been effected, it is assumed, has ceased, and the agent of injury is no longer operative; the reparative responses are evoked by the wound or defect, necessarily and constantly. They continue until the defect is more or less made good, and then they spontaneously cease as necessarily as they began, if no new or extrinsic interfering forces prevent. They are examples of an intrinsic efficiently acting automatic reparator, and in the result we see a *relation of fitness* to the organism or its part, in the quantity and quality of the product, and one of quantity mainly, often not solely, to the normal or casual massive injury or defect.

Such an intrinsic reparative faculty certainly can have been evolved by a survival of the fit, for without it survival could not be; and it has been well called by Burdon-Sanderson a "universal physiological law of nature."

This automatic character of the reparator is in all organisms in some measure local in its action, and is especially so in plants. It is necessary, and so it is never lost so long as life persists.

§ 45*f*. Even when some extrinsic intervening forces, or, as they have been rightly called, irritants, perturb it or misdirect it, still the vital responses occur; but then they exhibit different characters, in which can be traced in action the effects of both the intrinsic evolved faculties of the automatic reparator and the effects of the extrinsic or disturbing influences, both of which are then operative causal factors. The former are the self-same intrinsic faculties which were efficient in pure *Repair* when not perturbed, while in the latter they are seen to be acting inefficiently, and doing damage, because they are extrinsically perturbed; being then manifestations of the perturbations of the actions of the automatic reparator, and, like them, they are then only manifested by and through its vital activities, which must always persist, not only in the whole active focus of the process, but in each cell of it which so responds, even although such response, being misdirected, often results later on in a regressive series of changes, after having passed through a sort of provisional progressive series, which usually may have exhibited relations of fitness only to the irritant causes of irritation, and none to the suffering organism.

So, however, that at the periphery of the focus, where the extrinsic irritation and the resulting perturbation had been less, or may have been almost absent, the cells either retain or regain their efficiency as reparators, and then, through their activities of this order, *Recovery* at length takes place, so as to *Repair* the defects due to the primary injury, and also those due to the

damage done in and by the perturbation, or, as it may now rightly be called, the *Inflammation*; and this, just because the reparator is automatic in its action, and so endures while life lasts, even in or very near to the area which has been perturbed.

Thus, the reparator is operative not less in the inefficient and perturbed responses than in the efficiently acting ones; and it is also in each automatically and necessarily so; and, at least at the periphery of the focus in some of its cellular elements, at a later stage of the process, when the perturbing causes or irritants for any reason no longer dominate, it can and does at length become efficient, and then it brings about a *Recovery*, if only by a sort of compromise. The process of *Inflammation*, so thought of, is one which demands the co-operation of the automatic reparator as a factor even for those forms of it which involve regressions or a local necrosis in some of its stages.

But this statement does not carry with it any support to the teaching, that *Inflammation* itself is a salutary or a reparative process, or that it has been evolved as such by a survival of the fittest; for in all these cases the regressive responses are fitly related to the irritant, and damage to the organism is a constant, while the *Repair* or *Recovery* is not.

§ 45*g*. The "universal physiological law of nature" is, then, another term for the faculty of *Repair*, which every living cell or organism has evolved and must be endowed with; and its existence has to be accepted quite irrespectively of *Inflammation*, although *Inflammation* cannot be or occur without it. Such a faculty of *Repair*, and its necessary mechanism, the automatic reparator, is normal or physiological, and in this it contrasts with *Inflammation*, which is always casual, damaging, and abnormal. And this

is so, notwithstanding the fact that *Inflammation* demands for its occurrence the co-operation of the normal faculty of *Repair* and its mechanism, the automatic reparator ; acting, however, inefficiently in the presence of a misdirecting agent, the "irritant." While it is here thus accepted that the faculty of *Repair* has been evolved by "survival" of the fit," and it is denied that the same can be said, in any proper sense, of the casual damaging abnormal preturbations or disorders of this faculty, such as we see in an *Inflammation* ; which always does damage to the organism or its part in which the phenomena are observed, and it then antagonises or prevents *Repair ;* the only relation which can be traced between evolution or a survival of the fit and *Inflammation* is an indirect one.

It has to be sought for in the evolution of the faculties and mechanisms of *Repair* in the organism on the one hand, and in the evolution of the faculties and mechanisms of the irritant, especially when it is a parasitic one, on the other. When this has been done for each of the two main causal factors of *Inflammation*, *i.e.* for the intrinsic and the extrinsic ones, the result comes out, that for the organism inflamed the series of changes in *Inflammation* have antagonised or arrested *Repair*, or have caused further damage to it in the process, in a degree measured by the activity of the irritation ; and for the irritant, especially when it is a parasitic organism, have throughout been fitly related and beneficial to it. They may have even been often necessary to its existence under the conditions, and no doubt seems to me possible, that the extrinsic parasitic factors have always flourished, survived, and spread ; while the intrinsic reparative ones have been dominated in some ways, and may have even in an important degree often contributed to the survival of the extrinsic ones ; so that, in the apparent

conflict between the normal evolved reparative faculties of the organism suffering from *Inflammation*, and those of the parasite which is the extrinsic irritant cause thereof, the latter are always directly victorious, and the former are always vanquished. At least this is so for all established parasites.

Now, while it is correct to think and speak of the evolved normal faculties of both host and of parasite, nutritive and reparative, as necessary for each, and so as requisite to enable either to survive, it is not legitimate, and to me it is indeed inconceivable, to hold that a casual series of changes which always involves damage to the affected organism, the amount of which is measured by the said changes, can also be thought of as indicating similarly evolved faculties, such as Metchnikoff and his supporters have spoken of in treating of *Inflammation* itself as an evolved and a salutary faculty. So to argue, is to confuse *Inflammation* with *Repair*, which must not be, closely related though they are. For it is certain that *Inflammation* is a casualty, and is not normal, is itself always damaging and is antagonistic to *Repair* while it lasts, in the measure of its intensity and of the irritant actions within the focus or area of its phenomena, whatever may occur after it has ceased to dominate.

It is therefore not legitimate to consider such a series of changes as due to faculties evolved, as such, by a survival of the fit in the suffering organism ; rather must such a series be thought of as due to the disturbance or disorder of such beneficent faculties as the affected organism has been endowed with in its evolution, when, by a casual occurrence, they are more than balanced by extrinsic interfering forces, that is to say, by irritants ; and the fact that such forces, when they are included in a parasite, have been evolved, in no way weakens this conclusion.

Thus, the relation between evolution and an *Inflammation*, though a real, is not a direct one, as is the relation between evolution and *Repair*. *Repair*, so thought of as an evolved faculty of the organism in which the response occurs, as normal and physiological, is one which is sharply marked off from, and even contrasted, although closely related with, *Inflammation*, which is abnormal and a casualty, and not itself directly evolved, in the sense that *Repair* is.

§ 46. *Repair*, however, cannot, it must be granted, often be observed in its pure form in concrete examples. Therefore, it has to be idealised somewhat, as have many other general conceptions, *e.g.* a straight line or a true plane ; but a moderately careful survey of all organisms gives a sufficient basis for the idea of pure *Repair*, by showing examples of a gradual, and even of a near, approximation to the pure ideal.

If we think, as it were, of converging lines in one plane, which, if protracted, must at length intersect at some point which is, or seems to be, within a measurable distance, we see an example.

I may not here delay to give many illustrations of the stations along such imagined converging lines ; but a very few may be offered, and they will, I hope, suffice to make the idea sufficiently clear. Nearest to such postulated point of intersection of the converging lines, may be put such cases as those of a bisected amœba, in which the action of the injurious agent was brief, the injury inflicted was consequently relatively slight, in comparison with one of more complex organisms, in consequence of the smallness of the whole mass, its almost diffluent and homogeneous structure, the rapidity with which the breach of continuity is closed by liquid flow or elastic contraction, and the formation of a surface film by the physical and chemical

attributes of the cell-substance before nutritive responses proper, as they are commonly understood, can even begin; so that the wound or defect is, as it were, promptly protected against interfering irritating forces, parasitic or other; and the reparative faculties of each segment can begin and often do work effectively, given a normal environment for their nutrition.

Leaving out for a moment intermediate examples, I will take next one at the greatest distance from the imagined point of intersection, or the ideal of a pure *Repair*, say of a wound in man. If it be very small, as in the case of a clean needle puncture, so as to close promptly by the elasticity of the tissues, and if it be protected from interferences or casual irritant actions from without, and if it be not so placed as regards the internal structures as to involve important intrinsic sources of irritation, chemical, physical or other, it soon heals, and *Repair* is effected with little or no delay or disturbance of the process, and *Inflammation* proper can scarcely be said to occur, although some nearly passive effects of the action of the agent of injury, such as blood-clots, tissue-débris, and other such passive regressive or necrosed materials, almost always intervene, and so may *hinder* some of the operations of the automatic reparator.

These hindrances seem scarcely to act as irritants, and, perhaps in consequence of their intrinsic origin and close chemical relationship with the cells and tissue near, are usually not pathogenic, or not so in any such conspicuous degree as to extend the area, as do irritant actions proper. The automatic reparator as a whole mechanism, therefore, deals with them efficiently with a minimum of effort, and the responses, although they often exhibit some vascular and nervous excitation, and even deformity, yet do not present us with them in such a disorderly and excessive

degree as we meet with in any *Inflammation* proper in the same organism ; and this is shown by the fact that they do no appreciable damage, so that it may properly be said they compare rather with such grades of increased vascular and nervous phenomena as are met with in similar organisms in a normally occurring increase of functional exertion; as, for example, in a secreting mamma, or in a contracting muscle.

In such a case the increased vascularity near such a puncture, even although it has some resemblance to one sign of *Inflammation*, and that the most conspicuous one, is not truly a sign that *Inflammation* is present ; it is a sign only that the automatic reparator is actively at work, and is doing its work efficiently, without any concurrent appreciable damage to the part. The local determination of blood in such a case, although greater than in an uninjured part, is not greater than is serviceable to the automatic mechanism of *Repair* ; it is co-ordinated, proportionate, and efficient.

Such effusions of liquid and emigration of leucocytes as also occur are similarly proportionate and beneficent ; and the activity of the emigrated leucocytes as phagocytes is probably beneficent in disposing of the said hindering blood-clots and débris of tissues, or cells, either by englobing and digesting, or carrying them away to positions where they do not appreciably hinder repair ; and it may well be, that the leucocytes may sometimes profit by their food, so as possibly sometimes to be nourished by it, and so somewhere or somehow may grow and multiply ; but, in any case, they are not then pus corpuscles, and the process is not a suppurative one ; for neither the leucocytes, nor the tissues near which they are found, die or dissolve, nor are they disintegrated ; and whether or no they ever form new tissues, they destroy no living

tissues, and so they do good, and not harm, to the part, either of a suppurative kind, or otherwise.

Such a process, notwithstanding a certain superficial resemblance to *Inflammation*, especially to the less severe forms of it, *e.g.* the traumatic ones, is not itself an *Inflammation* ; it is rather very strongly contrasted therewith, as may be seen in the fact that it is beneficent, and only so ; and its apparent resemblance to *Inflammation* receives a sufficient explanation if we remember that both in *Repair* and in *Inflammation* the automatic reparator, whatever its mechanism, is engaged in the work, and that in the case here considered, as some hindrances, usually only of intrinsic origin, have to be overcome, it, in virtue of its automatic character, necessarily has to work more vigorously, and this is chiefly apparent in the increased vascularity of the part, with the necessary consequences thereof; although the question here remains perhaps open, whether the hindrances stimulate or irritate, and so impair the automatic character of the response.

Whether or no the hindrances to *Repair*, spoken of above, can and do really act as stimulants, and so possibly determine the increased action of the reparator, need not be further considered here, as I have assumed the reparator to be automatic—an assumption, however, not meant to be inconsistent with the possibility of such occasional stimulant actions by blood-clots and tissue-débris being sometimes active under some conditions of persistence.

Such vascular phenomena, however, although often so exalted as to be attended with some little redness, heat, swelling, and pain or tenderness, are not so inordinate or disproportionate as to impair ; rather they help the progressive cell-proliferations which the wounds or defects demand for their *Repair*. Cell-proliferation with develop-

ment therefore occurs, and as in quantity it is approximately equal to the loss or defect, and in quality it is very much like the responding or proliferating tissue, it ceases, so to say, spontaneously when the defect is made good, and with this the whole process which had been called into action ends, and there remains only obviously in the product, as a potential faculty of the living tissues, the automatic character of the reparator.

Doubtless, the stimulation of normal vital processes, here granted as possible, may be and has been thought of as "injurious irritation," and the response evoked as true *Inflammation*, or a perturbation of *Repair*. But the distinctions drawn here are, I think, sufficient, namely, that the responses are efficient, are not so misdirected as to do appreciable damage, and are not in this regard separate and distinct from *Repair*; as they do not antagonise it.

It is, however granted, that cases are frequent in which the reparative responses are mixed with some damaging ones, even although in the end these latter often cease; and the result is a *Repair* by a compromise, which outcome has been too much used as a proof that *Inflammation* is itself reparative. But such mixed cases are not correctly placed on the ideal converging lines.

Such a minute clean punctured wound in man is, then, to be compared in its healing, without any important break, with the *Repair* of a bisected amœba; although in the latter all vascular and nervous factors are wanting, and the proliferation is in it only of the structural units of cells, although reproductive regeneration may also follow, and new cells may be born.

§ 46*a*. It is perhaps scarcely needful to dwell here in detail on the other and larger injuries in man which are also repaired, and to which very similar remarks apply as

have been made on the example given of a small punctured wound. But, as in many cases the conditions are more complex, often are mixed, and, in proportion as this is so, the process of *Repair* is less pure, the responses then may include some phenomena more clearly like those which characterise an *Inflammation* proper, and may even with difficulty be separable therefrom, if at all; a few instances may be dealt with.

Examples may be seen in simple fractures of bones, in bruises, and in antiseptically treated wounds. After these traumatic injuries, the responses may show some, although relatively less important, evidences of irritation and of misdirection given to the automatic reparator; yet is the net result so markedly reparative, and so little damaging to the organism or to the part of it affected, that such evidences of damage are commonly and rightly neglected; and the process as a whole is considered to be one of *Repair*, that is, one of efficient action of the automatic reparator; and the product shows this in a distinct relation of fitness to the organism, even although in such cases the *Repair* may not be pure, but a sort of recovery by a compromise.

Thus, even these mixed cases justify the general conception of *Repair* as a normal faculty, a manifestation of a "universal physiological law of nature" evolved in each species of organism by a survival of the fit, in diverse modes and degrees, always beneficent to it, and showing always in the result of the process relations of fitness to the organism; so that in all these points it is in marked contrast to *Inflammation*, a constant character of which is that it antagonises *Repair*, and itself always does damage to the responding organism or part. The admixture so often seen in these cases, of some true *Inflammation*, with dominant efficient reparative responses,

does not justify any admixture of or confusion of the ideas of *Repair* and *Inflammation*, or sustain the conception of the latter as itself a reparative or a salutary response.

§ 47. Having thus given some illustrations of an almost pure *Repair* in the amœba, at a point as near as can be found to the point of intersection of the imagined converging lines, and again at the greatest known distance therefrom, that is, in man, the most complex of all known organisms; I must next give attention to some of the intermediate stations on these lines, where they diverge more than in the amœba and less than in man. For we may not forget that all organisms suffer casual injuries and need *Repair*, and can and do effect it in modes which vary much with the kinds, degrees and conditions of their evolved reparatory mechanisms; and thus that varieties of reparative phenomena dependent upon differences in the intrinsic attributes are met with and are very significant and instructive in connection with the complex and various forms of the responses to be studied, whether perturbed or not.

In the lower invertebrate animals and in plants, the *Repair* of casual massive injuries is very obvious and effective in its results; but our knowledge of the details of the process, and of the various intrinsic hindrances and perhaps of the extrinsic irritations which occasionally disturb its actions, and of the indications of the responses then evoked, is perhaps less than it is in man, and many of these disturbances are, I think, as yet unobserved, though present.

However, in all of these reparative responses we find that effective *Repair* is at length brought about by cell-proliferations and by a co-ordinated supply of growth-material, with a tissue development in due kind and degree such as benefits the injured organism, and so gives

a product which shows a relation of fitness to it. Such efficient products of the processes of *Repair* in these organisms are also most often, if not always, measured in quantity by the loss or defect due to the injnry; in kind they most often, if not always, resemble the tissue out of which they spring; most often, if not always, they cease as processes when the defect is made good, apparently spontaneously.

In these respects, the responses to massive casual injuries in plants, and in most of the lower animals, although they are all truly *Repair* responses, or manifestations of it of some kind, present some distinctions from those observed in man and in his nearest allies in the animal series. For the reparative faculties include also the regenerative ones, and are seen manifested often in the production of lost organs or members, and even individuals.

Thus, we often meet with in the lower animals, and plants, not only enough of new growth to make good a local defect of tissue, as in the closure of a wound, and in the effective coalescence of its parts, but also the regeneration of a lost organ or member, even if of considerable size and complexity of structure, which is not equally the case in the highest organisms. In these cases, the new growth and development of cells may persist long after the wound is closed or covered; and often they go on until the whole loss is replaced, when they also usually at length cease, at least as a local process of *Repair* or regeneration. But, in such cases also, the response is often measured somewhat in quantity by the defect, and is like in kind to the organs or members lost; and it also ceases as a local process, when the defect is effectively repaired; although the product can and often does afterwards grow and functionate, in common with the whole organism.

In some animal organisms, chiefly in the lowest, a type of regeneration, which may be called the reproductive, is met with throughout life; in some others, chiefly the higher of those which present it, these various results of a massive injury are met with only during the earlier life-periods, or it may be only in its larval states. The inference seems justifiable, that the lower animal forms, in their adult states, correspond at least in this regard to the larval phases of the higher ones.

§ 47*a*. In plants, somewhat similar, but not exactly the same series of phenomena, are met with after casual massive injuries, with a loss of organs or members; certainly we find, as in forest trees, in the overwhelming of a wound where a branch is cut off, that is, closure and *Repair* by a tissue regeneration; but such new tissue does not itself, as a mass, grow out into and form a new branch quite in the manner of a new tail of a salamander, or a new leg of a triton, or a new head or tail of a worm.

Younger axes and leaves, and indeed I think all young growing parts of plants, when wounded, heal without much delay or important interference from hindrances of an intrinsic origin, or usually from irritant actions of extrinsic causation; but the young tissue so produced does not as a rule, at the part itself, often grow and develop into an organ or a member or a part of one, like that which the injury may sometimes have removed; unless the part removed had been an axis; when, in the near neighbourhood of the wound, growth is liberated, and a collateral growth of new or old axes is then the equivalent of *Repair*, in what may well be called its reproductive variety.

What occurs more often in plants, is that the new young tissue which heals over the wound of an axis can give rise to one or many new buds, which may develop into as many new axes, by a reproductive *Repair*, each

bud having all the potential faculties of a perfect plant. These products, or responses to injury in plants, differ from the normal members which have been removed only in place and time, and it may be sometimes in number and dimensions; but their occurrence and order of arrangement are not constant or regular, and often the healed-over scar persists as such, especially if the new patch takes place in a parenchyma, when the *Repair* may be called simply a tissue regeneration.

§ 47*b*. Many of the lowest animal forms also respond to massive injuries in modes very closely analogous to those so frequently seen in plants; and thus we reach a great group of organisms, animal and vegetable, of which it is a common character, that massive injuries, even such as in the higher forms of life would be promptly fatal, are responded to by a repair process in which each fragment, even a very small one, can and often does reproduce a whole organism. This is the most highly developed form of reproductive *Repair*.

See, in plants, the moss *Funaria hygrometrica*, which can be propagated from very minute fragments, and the numerous examples given to us by horticulturists who propagate by cuttings, of which one of the most familiar and instructive is seen in the leaves of *Begonia rex*.

In some degree, this faculty of *Repair* by a reproduction of the organism would seem to be present in all or nearly all plants in some of their parts, if not in all, at least at some period of their life-cycles, and in varying proportions of their whole mass; but it is known that often such a faculty of *Repair* of casual massive injuries by a reproduction of the whole organism occurs also in very many of the lowest animals.

This has been long known and has been carefully studied in the hydra and in many other of the lower

animal organisms, especially in those which approach more nearly to plants in respect of the greater independence of their component cells, or cell-complexes. In the unicellular animals, it seems almost a constant faculty for the separated segments each to regenerate a whole organism from a segment of suitable structure and dimensions.

An amœba, if fairly bisected through the nucleus, would, there is little doubt, fully *Repair* each half, and so produce two complete organisms. If this has not been experimentally proven (as to which I am not able to speak confidently), it may perhaps in part be due to the practical difficulty of making such a section. Sections of *Stentor cœruleus*, in which the nuclei are multiple, even if into three parts, produce a new and complete organism for each segment containing a nucleus.

There is, in short, strong evidence to show that, under normal conditions of the environment, every artificially or casually divided living unicellular organism produces a new and complete organism for each segment so produced, which contains any considerable fragment of both nuclear-plasm and cytoplasm.

Perhaps there is even more evidence for this general statement in regard to unicellular animals than plants, and there may be some ground for thinking that the latter do not quite so quickly *Repair* after such an injury as the former do, and are perhaps more apt to die as a consequence; but it is known that some unicellular plants do *Repair* severe massive injuries in those cases in which some appreciable amount of nuclear-plasm, plus cytoplasm, remains in the segment, and this so as to quite restore the loss; and it seems to follow necessarily that, if in these each segment of a bisection contains such due amount of each plasm, then each one can become a whole and a complete organism, the *Repair* process being developed

by stages to a reproductive regeneration, its highest expression.

The doubts, sometimes expressed, as to the *Repair* of massive injuries of individual cells in plants, rest, I think, mainly on the facts observed in the component cells of the higher plants, which without doubt commonly after such injuries undergo only regressive changes themselves, and then such *Repair* as follows is due to the vital proliferative responses appearing in the nearer cells, not so injured. But in unicellular plants, as is seen in Vaucheria and in some of the Confervæ, *Repair* by a reproductive regeneration is, I think, accepted.

Speaking generally, I think in all organisms which normally sometimes reproduce the individuals of a species by a cell-division or by fission, a massive casual injury is repaired by a patch in that portion, the cells of which retain some uninjured plasm of both kinds; and if there be two or more such portions remaining, then each portion often completes the organism, and the result is a reproductive regeneration or *Repair*, which is in its result, and in the process, very much the same thing as a normal fission.

Thus, in both animal and plant unicellulars, *Repair* by a reproductive regeneration is to be regarded as a common though perhaps not a constant response to casual massive injuries in them. Whether or no *Repair* occurs in this form, depends mainly upon the extent or other characters of the injury, and upon the amount of uninjured cell-structures left in the segment—that is, on the injury and on the intrinsic *Repair* faculty.

§ 48. It seems a constant in all unicellulars, and also in the more complex organisms of both kingdoms of nature, that efficient reparative responses to massive injuries of any kind can only occur when the segment remaining has a

certain minimum mass, in which is contained at least the two chief essentials, the nuclear-plasm plus the cytoplasm, and also some stores of growth-materials, if the *Repair* response is to take on, or to proceed to, a reproductive regeneration, or even to an efficient regeneration of tissues or organs.

In any case, it is known that a separated portion of cytoplasm only, whatever other vital phenomena it may for a time display, does not ever develop so as to form a cell, and although it may exhibit the movements usual to the same part of the same organism, may close the wound, form a film or a pellicle on its surface, and even present some indications of an internal metabolism, very like those seen in a normal organism ; yet by these changes it rather shortens than prolongs the life of the part, as they use up its stores of matter and force, and thus, while the segment separated takes in and assimilates no new growth-materials from the environment, it is not viable, and cannot multiply.

Such a separated segment is as little able to effect a complete repair, as is the cut-off tail of a salamander, or the leg of a triton, or the several segments into which a lamprey is cut when it is used as bait ; and although all these exhibit for a time some of their usual vital phenomena, these are more wasteful than reparative ; and even if they may possibly also evince some attempts at cell-proliferations, yet is the whole segment as little viable as is the separated cilium of a flagellate unicellular.

These examples taken from vertebrate animals, in which a true reproductive regeneration after casual injuries involving separation of portions does not occur, find their equivalents also in many lower animals and plants ; in which, however, sometimes reproductive regeneration is not uncommon after injury, as in *Hydra viridis* and

Tubularia mesembryanthemum, in which we find that, notwithstanding the great simplicity of their structure, there is a minimum mass of it essential for the separated segments to regenerate, which they may do by reproducing the whole organism, as does the *Funaria hygrometrica*, and perhaps nearly all plants in some degree.

We are told that less than $\frac{1}{200}$th part of the bulk of a hydra cannot regenerate the organism when isolated as a segment, while it is well known that larger masses of it do so with great readiness and constancy.

It seems then that, apart from structural characters, except those of the cell itself, which are essential to nutrition and life, there is a minimum mass of living substance necessary for a true regeneration to take place, whether of tissue, organ or organism. This fact, as I take it to be, is probably best explained on the assumption that, for any segment or remnant after an injury to be repaired effectively, some stores of growth-materials are needful, and these are commonly greater in the larger masses; and this view finds support in the experience of horticulturists in propagation by cuttings.

§ 49. But besides the mass of the separated segment, there is another factor of almost as much importance in determining the extent and character of the regeneration it can present, viz. the intrinsic faculties of its component parts; for not all the cells and tissues, members, and organs of a multicellular organism, plant or animal, are in this regard equally endowed.

In the lowest organisms, plants or animals, constructed as they often are of colonies of apparently nearly similar cells, very little specialised, we know less of any differences which some of them may present in their regenerative faculties; so that each and all the component elements then seem to respond to casual injuries in a somewhat

similar manner. See the groups of Protophyta and of Protozoa, or the earlier embryonic stages of the Metazoa.

But, in both kingdoms of nature, we find, with increasing complexity and interdependence of structure, with differentiation of tissue and of function, some parts in which the regenerative faculty, whether of tissue, organ, or organism, is greater, and others in which it is less, or is apparently absent.

True, in all organisms, in all cases, regeneration of cells in the tissues is the most constant and widely distributed faculty ; and this implies the pre-existence of regenerative attributes in the component cells ; and in all such cases cell and tissue regeneration must coexist, and bring about a healing over or protection against adverse extrinsic influences, in order that a regeneration of an organ or of a member can be effective ; and thus it contributes to such regeneration.

In reproductive regeneration from a separated segment, casually or experimentally produced, some such more or less complete protection by cell and tissue regeneration appears to be a common, if not a constant, mode of beginning. Yet is this highest expression of the regenerative powers not quite simply related to the regeneration of organs or members ; it is indeed seen most frequently and completely in the lowest animal forms and plants, while the regeneration of organs or members is best shown in the organisms just below the highest ; and in the highest, we find only some forms of a cell or tissue regeneration persisting.

Of course, in unicellulars which have neither organs nor members, this mode of reproductive regeneration is not seen ; but in them it seems probable that reproduction by completion is nearly constant in each fragment, if duly composed of nuclear-plasm and cytoplasm in a

sufficient mass, so that structural unit proliferation can occur.

Reproductive regeneration, then, in the sense of a multiplication of the organism, after and due to a massive injury, is indeed met with, but only in the lower forms of living things; and then it occurs in the course of and as a consequence of a regeneration of cells, tissues and organs, after their injury or removal, so that an organism often is thus completed, while yet it is not so directly multiplied. Such a completion of an organism, of which examples are seen in earth-worms, which can produce a new head and a new tail after their removal, and in many other lower invertebrata, vascular and not, seems often to end the series of events, in as far as they are directly related to the injury.

The organ or member regenerations seen sometimes in vertebrata belong to the same category; they tend to complete the organism, and may often render it viable, but they do not ever directly multiply it, though, as a later consequence, normal multiplication is thus made possible.

It is only in the lower animals, and in plants, that small and separated fragments or segments of an organism can each become a complete new organism; but when this occurs it is often largely by a process of completion for each fragment, so that it does not differ in essentials from that spoken of above, in which an earth-worm produces a new head end or a new tail. This conclusion applies in essentials both to animals and to plants, to a segment of a hydra, or to a willow cutting.

There is reason to say that these organisms, probably all organisms, possess such regenerative or reparative faculties in some parts or tissues in a high degree, and in others much less so, or possibly not at all. Thus, in

most, probably in all, the organisms which multiply in number in response to some grave injuries; as well as in those higher forms which only complete the individual, and may make it viable; we find evidence that some parts of their structures are specially endowed with the required regenerative attributes of any of the types.

In the earth-worm, which does not regenerate a whole organism from every segment wherever the section is made, a region exists near the head, and another near the tail, in which the faculty of regenerating the lost parts is present and efficient, while this is not so beyond or outside it.

And correspondingly, in the hydra, which exhibits in such a high degree the faculty of multiplication of individuals in its regenerative responses to grave injuries of most parts of its body, does not do so equally in all; for a separated tentacle, although it can live a while, and may possibly, even probably, present some temporary and futile regenerative responses, does not regenerate reproductively; so that it dies before long, although its mass is often greater than that of some separated segments of the body which can reproduce a complete hydra.

Thus, from hydra to man, and from moss to oak, the component parts are endowed with different degrees, and it may be with different kinds, of responsive regenerative faculty to casual injuries. It is thus shown to be possible, as on other grounds it may be thought of as probable, that certain structures, even in the highest and most complex organisms, are specially endowed in this regard, and may have, as one of their functions, the *Repair* of a casual massive injury, in some mode, by a regeneration of tissues or of organs, and either complete or incomplete.

I have already given reasons for thinking that in higher

plants the cambium, and in vertebrata the vascular connective tissues and epithelia, are so endowed; and to this I may now add that in the lower plants and animals, even in those which have developed from a bilaminar blastoderm, there is observable some, although perhaps less, specialisation of the reparative apparatus and functions, of this kind.

Such a specialisation of function and structure, it is not difficult to see, might be very useful to an organism in its struggle to exist, and it may therefore rightly be thought of as part of an evolved mechanism of *Repair*, in which may be included the circulatory apparatus, and with it would also be involved phagocytosis, there seems ground for thinking, at least in the higher organisms.

The instances met with in plants, as well as in animals, in which particular regions and tissues are thus specially endowed with reparative and regenerative faculties, are perhaps most conspicuous and striking where a provision in advance is made for an event which in some cases occurs physiologically and regularly, and in others as a casualty, and these are to be regarded as strongly corroborative of the view above advocated. Thus, excluding the fall of the leaf and fruits, and also the allied phenomena in some of the lower animals, as being regular and physiological, I would point to the provision in advance in many forest trees for a repair of the wounds caused by fallen branchlets, the fall of which is a casualty, and yet is there found, at the part at which the breach of continuity takes place, a specially endowed tissue which ensures an early *Repair*; although the case is pathological in some degree.

Perhaps even more striking are those cases in animals, in which some crustaceans and echinoderms readily break off a limb or a ray when it is injured; and do so

at a part where there is a local provision in advance for a prompt *Repair*, usually in these cases organ or member regeneration, rather than at the part actually injured.

It may be said, therefore, that all organisms *Repair* casual injuries as well as normal ones; and in so doing, often tend to complete the original form and structure by restoring the loss; that this applies to unicellulars and to multicellulars, to animals and to plants; that, as a result of each such *Repair*, the individual organism which had suffered loss is often completed, and so it tends to become viable; but it does not do so directly, or constantly, and it does not always so multiply the organism; while the separated portions of such an organism, if not capable of a similar faculty of completing an individual, die after a short period of a futile vital effort, such as we see in the cut-off ends of a stylonichia or an earth-worm, the amputated limb of a triton or of a man.

Some, however, of the cut-off parts isolated from the main mass of some organisms, are capable of completing an individual organism, which parts may then be viable; and in these cases the regeneration is at least indirectly reproductive, and so, out of grave injuries as factors in the causes, there can thus spring, as a later effect, a multiplication of viable organisms, given, certain conditions of the injured organism, of its segments, or fragments, and of the environment. Such reproductive regeneration is seen, as has been said, commonly in unicellulars, but, perhaps in consequence of the greater facilities for observation, much better in the simpler multicellular animals—only, however, in their lower forms; while in plants it is seen, up to the highest and most complex forms, as in ordinary propagation by cuttings.

In all cases, reproductive regeneration demands, as has been said, a certain minimum mass of the organism in the segment isolated, and the presence in it of certain structures, of which the most constant are nuclear-plasm plus cytoplasm, which alone may suffice for unicellulars, and perhaps also for some of the very simplest aggregations thereof. It may be that even a segment of an amœba demands a certain mass of store growth-material, as a condition of its regenerative reproduction. But, in multicellulars of more complex structure, up to the limits within which it can occur at all, reproductive regeneration demands the presence in the separated fragment also of complete cells, with all their faculties and growth-materials.

These organisms in the lower forms, whether animals or plants, are very little differentiated and specialised, as is seen in hydra and in funaria; but they, as a group, given suitable cultivation conditions, can then produce a new organism for each segment, usually by completing, in some mode, each fragment into the form, and with the attributes, of the original organism of which it was a part.

In the higher animals such reproductive regeneration is unknown, as the structure and the attributes of the organism become more complex and specialised. In crustacea, batrachia, and reptilia, it is represented only by organ or member regeneration; and at length in the highest, in man, by cell and tissue regeneration, which resolves itself finally into a cell-proliferation with development. It is mainly in regard to cell, tissue, and organ regeneration, that it can be said *Repair* of casual injuries is commonly effected by more or less specialised parts, so endowed as a result of evolution and a survival of the fit; for in the reproductive regeneration, as above it has been spoken of, it would seem that, the less the specialisa-

tion of the parts, the greater is the aptitude of each small separated part to grow into a complete organism ; and pathologically, or in the *Repair* of injuries, reproductive regeneration is less markedly limited to particular parts or tissues. In some higher plants, as in willows and poplars, it is true, there is some, though only an apparent, contradiction to this general statement ; seeing how readily they, in the course of their *Repair* of grave casual injuries, reproduce the organism, usually by or through a process of completion.

The contradiction is, however, in these cases more apparent than real, for in them also the first and most constant response is a cell or tissue regeneration, after which follow organ and member regeneration, and at length sometimes a reproductive regeneration ; usually, however, only as a later result of the growth and development of a regenerated organ, which is sometimes itself only an awakened growth of a pre-existing, but dormant, bud-germ ; although sometimes without doubt a newly formed one, as is well shown in Hartig's experiment.

§ 50. *Repair*, then, it may be repeated, is another name for "the universal physiological law of nature," and almost a synonym for the more ancient "vis medicatrix naturæ," and within its meaning I here include all the regenerations. Starting from the physiological idea of nutritive repair of waste and of functional expenditure, and assuming the persistence of this faculty as an essential of life, however long and profoundly it may under certain conditions slumber, it may be said that the "universal physiological law of nature" is seen in operation in all regenerations, normal and abnormal, after a normal or a casual injury to a cell or a tissue or an organ ; and *Repair* is manifested then in all cases by proliferations of structural units of cells, or of cells themselves, or of both,

with a subsequent development, and it is effected by the regenerative reproductions of units of both orders.

This conception excludes, or does not include, the idea of *Repair* or of regeneration, as a truly pathological one; and although, in *Repair* or in regeneration after casual injuries, the injury, the condition precedent, was abnormal, the process itself is here thought of as only a normal one; not less so than the very closely allied one of the *Repair* of normal injuries, which are often massive, and are seen in all organisms, especially during growth and development, resting upon the same faculties, and manifested by essentially similar phenomena.

In this way, a sufficiently sharp line of distinction is drawn between *Repair* and *Inflammation*, the antagonism of one with the other is made comprehensible, and is still consistent with the doctrine that the reparative faculties are presupposed in *Inflammation*, and are even effective agents in producing the damage, seen in the fifth sign, so constant in it, under the misdirection of the irritant actions.

Regeneration has, however, been studied very much as if it were not a part of *Repair*, and very much as a separate subject; yet has it been so freely acknowledged that it is reparative in its effects, that I make no apology for here dealing with it as a part of *Repair* in a wide and proper sense of the term.

Regeneration after casual injuries may conveniently be grouped into three main forms, which, when compared and legitimately combined, help, I think, to a clearer conception of *Repair* in the broader yet true meaning of the word. (*a*) Thus, a regeneration of lost parts of a cell or of a tissue is the *Repair* of the same, in which a defect is made good, or approximately so, by a proliferation of the structural units of a cell, or of the cells themselves,

with subsequent development, given normal conditions of environment, and of the responding remainder of the injured organism. This form is universal in all organisms, and in all the three forms of regeneration. It often occurs without the other forms ; but these are never found without it, so that it is often met with alone, even in the highest organisms, at least in the adult, in which the other forms do not, or may not, occur. It is always efficient.

(*b*) Regeneration of lost members or organs after casual injuries is a *Repair* of the organism in which the lost parts are restored, the organism is completed, and may thus once more become a viable whole, by a process which includes the above-named proliferations of structural units of cells, and of cells, with development into tissues, as in (*a*), and it includes manifestations of what may have been designated by Virchow's expression "formative force," under the normal exertion of which the regenerated mass takes on the form, dimensions, structure and faculties of the lost parts. It does not occur in all organisms, or in all parts alike of those which may display it ; it is absent in the highest and most complex of all, and it is better seen in animals below the highest, and above the lowest. It does not occur in the highest, apparently because in them the organs and members are too much specialised, and have lost, or have not acquired, this faculty ; and perhaps, because in them the greater relative efficiency of (*a*) renders it less important. It is well marked in plants. It does not occur in the very lowest organisms, for the sufficient reason that they have neither members nor organs. See the unicellulars and the simpler aggregations thereof.

(*c*) Regeneration of organisms, or reproductive regeneration after casual injuries, is the *Repair* of the organism, in which lost parts are restored, the organism is completed and rendered viable, not only as in (*b*), from the

remaining principal mass, so as to complete the individual, but also from each one of two or more, often very minute fragments of one organism; and thus a multiplication of individuals may occur, each of which is viable, if the cultivation conditions be suitable. This is effected by a process, or series of steps, which are often in essentials the same as those in (*a*) and in (*b*); so that in it we find proliferations of structural units of cells, or of cells themselves, with development into tissues, and a further growth and development into other tissues, and also a growth with development into organs or members; until from each fragment a complete and viable organism results, unless the fragment had contained less than the needful minimum mass; and this process, it may be said, occurs under the direction and guidance of the "formative force" of the organism.

Subject to the adequacy of the mass, and also of the structure and composition of the fragment, and of the cultivation conditions, a multiplication of individuals thus depends on the injury, or the position of the section, say of a stentor or of a stylonichia, and such a faculty of regenerative reproduction is useful to the species.

This reproductive form of regeneration is seen only in the lowest animals, and in plants. Such a reproductive regeneration, however, somewhat resembles normal cell-division during the life and growth of tissues, and was thought of by Virchow, and since his day by others, as implying necessarily the death of the dividing or proliferating cell; but this is not, I think, a tenable doctrine, for the dividing cell is always exerting a normal living faculty, and the result always is an increase in the number and in the quantity of living things. It is absent from many of those organisms of an intermediate station, in which organ or member regeneration is more common.

There is some reason to think it may be associated in those organisms in which it does occur with a persistence in them of a faculty of reproduction by fission, but this I cannot affirm with confidence.

In plants it is much more widely spread than in animals; it is, in fact, almost universal in them, although even in them it is most marked in the lowest.

In these remarks, I have dealt with reproductive regeneration when seen in detached fragments of an organism, as if it were always and solely brought about by a process in which an injured part is first completed to a normal phase. But this is not, I think, always so, and sometimes a new organism is said to be produced from a new meristematic group of cells which afterwards develop.

§ 51. *Repair*, then, is thought of here as including regeneration in all the three modes given above, as having for its most constant factor efficient proliferation of structural units of cells, and of cells, and tissues, and as being an evolved intrinsic faculty, liable to be perturbed in all its modes; and when it is perturbed by "injurious irritation," as presenting us with that series of changes we know as *Inflammation*; which itself is not here accepted as a directly evolved or normal faculty. But it is not herein said, or implied, that all the almost infinitely varied modes of disturbance of *Repair* which are met with in nature, however conditioned, are rightly to be considered as manifesting *Inflammation*.

Doubtless, it would be quite consequent to group all the modes of damaging and inefficient *Repair* processes in one greater common category, which could be held to include the *Inflammation* process with others; but it would be at least equally legitimate to place some of them in a different category of less width, or in a separate group; that is, those exertions of the reparative faculties

which are otherwise inefficient, and to which, at least provisionally, may here be given the name of abnormalities of *Repair*; the characters, if not the causal factors, of which enable them to be distinguished from *Inflammation*, though they are certainly very closely allied thereto in some very important and even essential respects.

Provisionally, then, I adopt this expression, *abnormality of repair*; and separate these abnormal reparative responses and processes from those which are due to a perturbation of *Repair*, are excited by "injurious irritation," and are here known as *Inflammation*; and I place them with the malformations in the domain of teratology, and assume that in them "injurious irritation" is not a constant or an essential factor in their etiology. The expression, "abnormalities of *Repair*," here provisionally adopted, and distinguished from the "perturbations of *Repair*," is, I grant, open to criticism; and hence its use is only provisional. I might have used the expression, "inadequacy of the reparative faculties of structures"; but I adhere at present to the term as above adopted, because it is more comprehensive, and although not altogether satisfactory, I cannot mend it.

To some slight extent, therefore, I must now qualify or limit the expression "perturbation of repair" as it was used in my attempted definition of inflammation in the address "On Some Diseases of Plants compared with those of Man (1892, and reprinted 1903), in which no adequate attention was given to malformations, or to their etiology, and no sufficient separation was made between them and *Inflammations*. These abnormal modes of reparative responses, or of some of their near allies, have already been spoken of, and grouped among the reparative regeneration phenomena, in (*b*) and (*c*), *i.e.* those which include organ and organism regeneration,

if they are imperfect, or from any causes or conditions inefficient; and it is beyond doubt that some of those placed in group (*a*) are also present in the focus of change, when the needful conditions for an efficient *Repair* are not present.

§ 51*a*. The malformations, or abnormalities of *Repair*, are etiologically not well known; perhaps they are not possible to be so in all organisms; they do not all of them, and always, show well any damage done in the process, or by it, although they often do so, whatever may be shown in the ultimate product, as a consequence of some probably past event or injury. As a whole, they have been studied chiefly in connection with teratology, and very much apart from their antecedent or concurrent conditions or causes, of which but little is known.

It is therefore, I think, expedient to limit here the use of the expression *perturbation of repair*, in its relation to the *Inflammation idea*, to those damaging or inefficient reparative responses to irritant actions or "injurious irritations" persisting in the focus, and resulting in a product showing relations of fitness to the irritant; and so therefore to make it a technical one, and to use the expression *abnormalities of repair* also in a limited and technical sense, for those other varied and inefficient reparative changes which are otherwise caused and conditioned, in modes which are but little known, and yet demand careful attention.

They must be distinguished, however, from the responses to "injurious irritation," which is a constant condition precedent and concomitant of an *Inflammation* proper. In this way a sufficiently well-marked distinction, I think, can be drawn, between the inefficient and almost always damaging series of changes met with in mal-

formations, and those we know of in *Inflammations*, which also are always damaging. For in the former, although they are also due to the inefficiency or inadequacy of the intrinsic reparative faculties, as conditioned, they are not always determined by, or directed by, persisting concomitant "injurious irritant actions," or related fitly in the results to the irritant; they show no specific relations to a persisting "injurious irritation," and from our very general ignorance of the injuries or conditions assumed to have caused them somehow, we can trace in them neither quantitative nor qualitative relations to the initial injury, such as we can find in the efficient reparative responses of *Repair* proper, nor any similar relations to extrinsic injurious irritant actions.

The common and convenient practice is to classify malformations in accordance with their anatomical characters, without much or definite reference to their etiology, which is indeed too little known.

Thus, I defend and justify at present the separation above given of the expression "perturbation of repair" from abnormality of it, and use both the former and the latter in limited and technical senses; so, however, as to remember always that in nature processes are often very much mixed and overlap, and that, in many teratological processes, true *Inflammation* is very often associated. It will, I hope, be shown in the following pages that some at least of the conditions precedent, *i.e.* the causes of malformation processes, are traceable in the effects, that is, in the characters of the response, in its phases of development, and in the extent and characters of the injury possibly seen in it; that is, the causes may be seen as frequent, if not constant, antecedents of such events; and thus some little approach is at least attempted, towards an intelligible etiology

of malformations, as well as a distinction drawn between them and *Inflammations*.

It has been said above that, in the more or less efficient reparative regenerative phenomena, as grouped in (*b*) and (*c*), those of the group (*a*) also are constantly present in all, *i.e.* both in the efficient and the inefficient responses, at least in some grades, and with some recognisable characters; so that in all, the *Repairs*, the perturbations and the abnormalities of it, the (*a*) responses are never wanting, and thus they may serve as a connecting link for all the members of the groups of reparative responses, and of the inflammatory and teratological ones; and it is noteworthy here that they are met with in all living organisms, which cannot yet be said of (*b*) and (*c*), or confidently of malformations generally. The characteristics of the responses to perturbations of repair determined by irritant actions, *i.e.* in *Inflammations*, and seen in all living organisms under certain conditions, are thus associated always with some proliferations of structural units and of cells, with developments thereof, often specific; and yet they differ appreciably from the progressive and proliferative phenomena seen in the teratological processes, although both series contain very closely allied proliferative changes; and the casual conditions determining their production differ, in abnormality of *Repair*, from those which determine a perturbation of *Repair* or *Inflammation*.

In the teratological abnormalities of a repair process, then, the regenerative series of events placed in group (*a*) are as essential and constant as they are in the perturbation responses after "injurious irritation," and called *Inflammation*, or in the efficient process of a simple *Repair*. In all, we have operative the evolved intrinsic reparative faculties which all organisms possess, although differently conditioned, and in all the parts live.

It comes out, then, that the processes met with only in some organisms, and under some relatively fewer conditions, are less universal, and form a narrower category, than those which are present in all living things, while they live. The teratological group of processes is thus in a narrower category than the intrinsic reparative ones, and than the *Inflammatory* ones.

The teratological abnormalities of *Repair* which result in the production of malformations, and sometimes, not always, are seen among the regenerative groups (*b*) and (*c*), are frequently limited to parts of an organism, or to some only of its phases of development, and then are obviously dependent in a great degree upon the evolved intrinsic reparative faculties of the organism, or the part of it affected, at that stage of its life; but in part also upon the initial injury of the organism, that is, on the causal conditions.

So that ova, embryos, larvæ, and younger, as yet imperfectly developed, tissues or organisms, or parts of them, which so often give us examples of the production of malformations, in a very close alliance with the regenerative forms (*b*) and (*c*), do so largely in dependence upon the exceptional intrinsic reparative faculties which mark that phase of their life-cycles or that structure, and show, at least relatively, a much-reduced liability so to react, in the more adult tissues and organisms.

It should here be remembered that pure *Repair* and its perturbation in an inflammatory response are also met with in ova and in embryos and in immature parts of tissues, as well as malformations; and that it is not an exclusive or diagnostic feature of a malformation to be produced in such a nidus, or to be congenital, or hereditary, as is often said; although it is, I think, true to say that teratological products are more frequently congenital, and hereditary, than are inflammatory ones.

Here have been given, I think, sufficient grounds for the expediency of separating the study of abnormalities of *Repair*, or malformations, from the perturbations of *Repair*, or *Inflammations*, and of pure *Repair*, with the proviso, that all the processes are very intimately associated, and have, for a common and essential factor, the evolved intrinsic reparative faculties present in all organisms, and also always present various proliferative phenomena. A reason is also given herein for such a separation upon more logical grounds than mere expediency, and indeed such as show some of the essential distinctions between the products of an *Inflammation*, of a malformation, and of a *Repair* proper.

§ 51*b*. It will be interesting here to give some examples of malformation production, seen in some regenerative responses, and to trace their etiology as far as is possible; although it is granted that a satisfactory etiology is not known.

See, for example, the cases in which, as in a hydra, or a tubularia, or a plant cutting, the segment separated is unable, either from its too small mass, or from its incompetence in structure, or in composition, to produce a viable organism, even when cultivated under good conditions, and although competent to grow and to develop an imperfect approach towards the normal form.

In this respect it is convenient to study first the conditions which may determine the production of abortions. When the separated or injured responding thing is too small, or imperfect in structure, or composition, then any product of an inefficient regenerative attempt at the reproduction of an organism from it would be rightly called an abortion, and it is in some respects distinguishable from other malformations, while it can scarcely be rightly called a perturbation of regeneration, or a misdirected effort at *Repair*,

such as I consider *Inflammation* to be. Rather, it is to be thought of as an abnormally inadequate product of a reparative process, in which the requisite conditions for adequacy had not been given, or were themselves inadequate.

A viable organism cannot arise out of an ovum, or a segment of one, or out of an adult which for any reason did not contain one potentially, suitable conditions of the environment being granted. The abortion, however, although not viable, does usually present us with some indications that it has made an attempt, even although a futile one, to produce a complete organism, and this is shown in its form and structure.

In this respect it is marked off, though often by not very sharp lines, from the simpler regressive changes seen in a still smaller and less competent separated segment, as a detached cilium, or a fragment of cytoplasm, quite free from nuclear-plasm, or in the more complex and larger tentacles of a hydra, or in the separated ends of an earthworm, the limb of a triton, the muscle-nerve preparation, or the separated heart of a frog, in all of which, even although in some of them there may be, and I think must be, some little admixture of a proliferative effort, or production of structural units, and even of cells, especially in the larger and more complex masses of tissues and organs, which functionate for a while; it may be said also there is a regression, and a passage through many stages to necrosis, and disintegration.

See, for an example of a dwarf production, the figure of *Tubularia mesembryanthemum* given in his *Regeneration* by T. H. Morgan (1901), which shows the minimum segments of a cleaving ovum which can present reproductive regeneration, and the changes met with in those below the efficient minimum size. Such a malformation is closely allied to an abortion.

An abortion, then, would seem to be the result of an attempt to reproduce an organism out of insufficient or unsuitable structures or materials, which attempt fails partially, but yet so far succeeds as to show in the product some semblance of the perfect form, enough to enable it to be recognised, but not enough to enable it to survive as a viable organism, even under the best possible conditions of the environment; and it is for these reasons that its changes are in part at least regressive ones. Such an abnormality of *Repair* it is necessary to exclude from a perturbation of *Repair*, as related to *Inflammation*, in the sense in which it is dealt with here.

But it must be remembered that in concrete cases such an intricate admixture often occurs, and such numerous and delicate transitions are met with, that it is often difficult, if not impossible, to say confidently of an individual example, whether it is an abortion or some other mode of malformation, or an *Inflammation*, or all three mixed up.

Gradations are found, at one margin of which minimum segments or fragments occur which attempt to produce an organism and fail, but pass on through an almost infinite series of grades into complete and sometimes apparently viable, but dwarf products, which are therefore not simple abortions; and at another margin occur abortions proper, passing through an equally numerous and delicate series of stages to a regressive series of changes which involve necroses; and even within the regressive series of changes there are included often, perhaps always, some proliferative phenomena of structural units of cells, and of cells themselves, which are usually called progressive; and yet in these cases also, they are so only for a brief space of time, so that in the end they may perhaps have tended to shorten rather than to lengthen

the life-period of the fragment, much in the way that certain functional efforts such as movements do ; and yet, like the said movements, they were necessary consequences of the evolved intrinsic faculties of the cells, cell-components and complexes, acting automatically, yet doubtless somewhat influenced by the conditions, paradoxical as this may seem.

In all these cases of abnormality of *Repair* and of malformation production, "injurious irritation" of the fragment, which should be thought of as undergoing a form of inefficient reproductive regeneration, or as making a futile effort so to regenerate, and as suffering mainly a regressive yet complex series of changes, is assumed to be absent, and the conditions in the environment are assumed to be adequate for nutrition and proliferation.

But this is not often or always so simple in nature ; and when injurious irritant actions do intervene, it appears from observation certain that they are responded to by the fragment, in part, according to the amount and character of its then possessed evolved reparative faculties, which in the last stage of the regressive series of changes, namely, necrosis, were nil, and in the stages near but prior to this were slight, and in the progressive or formative stages were more active and obvious, and in part according to the influence of the irritant actions. Then the responses are also directed, or rather misdirected, by such "injurious irritation," so that we should then have a true *Inflammation* as an admixture in the process of the production of an abortion, but not as a necessary part of it. Such admixtures are, in fact, very common in nature, and they illustrate the close relation in essentials of teratology and of *Inflammation*.

§ 51*c*. It is convenient to study next the conditions which determine the production of dwarfs. The cases in

which, from an egg, a single blastomere, or a segment of a blastula, an apparently perfect but dwarf embryo is formed, are also of great interest in this connection; and as they are all forms of an attempt at a reproductive regeneration, set up by casual injuries, in an incomplete part, their relation to the abortive products of abnormalities of *Repair* must be here considered. Dwarfs may sometimes be viable; but abortions never are so.

The evolved intrinsic attributes of the thing which is irritated, and so is perturbed and responds, are essential factors of such responses in *Inflammation*, not less so than are the perturbing agents, the irritants, and their attributes; and observations tell us also that in some very important respects the evolved intrinsic attributes of a fertilised ovum, and of its immediately following phases, differ so much from those of the other cells, more especially from those of the tissue-cells which are the components of adult and complex organisms, that it is requisite here to indicate such differences, and some of the effects thereof, in modifying the responses to a simple injury; and a like conclusion is to be drawn in respect of the responses to the abnormalities of *Repair*, that is, to the production of malformations such as abortions, and dwarfs.

A fertilised ovum, say of a sea-urchin, bisected, behaves somewhat like a bisected amœba, or a stylonichia, or a stentor; in that a segment containing the nucleus completes the cell, or the organism; and a segment devoid of a nucleus does not, unless it be separately impregnated by a single spermatozoon, which may happen, and then it, the spermatozoon, seems to take the place of a nucleus.

Each cutting or segment, then, produces at length an apparently complete free embryo, which, after first passing through the phases of cleavage, of blastula, and of gastrula,

produces in each case, as a result, a free embryo which is a dwarf, and may perhaps be, but is not always, viable. On the whole, I think it would most often not be viable; if so, it would be, or a near approach to, what I have spoken of above as an abortion; and then gradations are often found between it and a dwarf.

Suppose the non-nucleated cutting to be not impregnated, it regresses as does a fragment of cytoplasm cut from an amœba; then, the nucleated portion alone completes an organism, and we have a case of *Repair*, without a regenerative reproduction, in the sense of a multiplication of an organism.

However, the nucleated cutting of the impregnated ovum, in developing and differentiating its part into a free embryo, produces then only a dwarf, which is doubtful as to its viability; while the nucleated cutting of an amœba, or of a stentor, although also at first reduced in mass, is viable, that is to say, it is able to live and prosper, in the environment; and there, acquiring new growth-materials and conditions, completes its bulk and structure, and soon propagates its kind. It has not first to pass through appreciable phases of development before it can feed and grow, as the fertilised egg-cutting has to do; but it is saved this expenditure, which seems to exhaust very much the stores of growth-material or of energy in the egg.

Such a bisected fertilised egg, therefore, differs from a bisected unicellular organism in that it is less constantly capable of such a complete regeneration as produces one or more viable individuals; and it is subject to the necessity of first passing through certain phases of development before it can reach that measure of individuality of life, such as is seen in the free larva, before it can derive the necessary growth-materials or energies for

such further development from the environment, or from the stores thereof possibly present in the cutting itself.

The fact, however, that in ova such intermediate developmental phases are constant, in the segments, and the fact that, in the event of the production of a definite specific form and structure, these are always produced by a regular series of differentiations, further distinguish the phenomena seen after a bisection of a fertilised egg from those seen after the bisection of a unicellular organism, show that the former is endowed with some characteristic, intrinsic, important attributes, not appreciably present in the latter, and so that it differs, perhaps still more widely, from the regenerative proliferative attributes of the tissue-cells of complex adult organisms. Such differences in the intrinsic reparative attributes of the organism or part injured demand careful attention in studying the responses to injury, or to "injurious irritation," effected by the automatic reparator, of whatever kind or structure; and this is so also of all the phenomena seen in malformation production, after abnormalities of the reparative faculties.

The observations made by bisecting a fertilised but not yet segmenting egg show clearly enough the dependence of the resulting free embryos as regards size upon the mass of each fragment, or of the cutting which reproductively regenerates; but this fact, and some others, indicating a distinction of importance between the regenerative responses of a fertilised ovum or an embryo, and those of free or tissue-cells, or of free adult organisms, unicellular and not, are better seen in the results of observations made on separated blastomeres, and on sections of a blastula, or on the gastrula stages of embryonal development, especially in the invertebrata.

Thus, it appears established that the bulk of a free

embryo, so produced, is proportionate to that of the separated fragment of a segmenting egg; so that this bulk is half the norm when the newly regenerated embryo is derived from one of the first two cleavage-masses or cells; and when, as may happen, a gastrula stage of the embryo is developed from a blastomere, only one-sixteenth of the whole ovum, the resulting free embryo has the same proportion, if it then develops an embryo at all. But it is clear that the chances of producing a free embryo at all are greater with the larger blastomeres, and less with the smaller ones; and the chances of viability of such embryo diminish as does the size of the blastomere out of which it springs. So that the mass of the segment is a very important factor in the production of abortions, or of dwarfs.

A very similar result appears after sections of the blastula stage of an echinoderm ovum, and, though less clearly seen, it comes out also at the later, or gastrula stage; and in all the bulk of the produced embryo is proportionate to that of the segment which produced it in either stage; but the specific form and structure of the resulting embryo are approximately the same in all, excluding, of course, casual interferences, and the chances of survival for the resulting free embryo diminish as does its bulk, until, it would seem, they are at length lost as the mass is reduced.

At whatever stage of the egg or embryo the section is made, the final result is the same; it is, if not an abortion, a dwarf or a reduced copy of a normal embryo; but the series of phases through which it passes in attaining this end varies; so that it is longer when the section was made at an earlier stage, and shorter if it were made at a later stage; and so a small segment of a gastrula produces a dwarf free embryo by a series of changes briefer than, but

otherwise much like, those of the later stages, after a separation of a blastomere or a section of an impregnated ovum.

§ 51*d*. Up to the time of the production of the free embryo or larva, all the true growth-material which went to the making of it seems to have been contained in the one fertilised ovum ; and yet out of it may be produced one, or perhaps sixteen organisms, all alike in kind, form, structure, and faculty, though unlike in size, in viability, and in chances of survival.

After the production of the free larva comes in at least the chance of added growth-materials from the environment, and in normal cases this chance is great as the free larva is large. I have here intentionally left out of consideration the supplies of water, oxygen, and heat, which are known to influence the developmental changes in a normal ovum, as they are not specific, but common to all.

Note here that the multiplication of individuals possibly so resulting is in some degree an effect of an injury ; it is an instance, a very interesting one, of a reproductive regeneration ; and each organism so reproduced, whether from a single blastomere or cell, or from a group of cells, in a segment of a blastula, is so by a reparative regenerative act, in which sometimes each separated part can complete a whole organism by repairing a defect out of its own stores of growth-material only, and then by a series of steps determined by its own intrinsic faculties ; but it is then not always viable.

It is important to remember also that a free larva produced from a single blastomere is so after the blastomere has by segmentation first multiplied itself ; but one produced from a segment of a blastula which has already passed through the phases of segmentation is so without

further cleavage; we are told, also without any appreciable further cell-proliferation, and only by a simple change of form or by a rearrangement of the structural elements present in the segment.

The facts given in support of this last statement seem to me to demand confirmation in some respects; but, as it is, I think, fairly well established that the number of cells which go to form a blastula is proportionate to the mass of the original segmenting ovum or blastomere, out of which it is formed; and, as the size of the blastula resulting is so also, while the form and structure of the free larva are approximately constant in the larger and in the smaller ones, the inference is apparently well founded that the multiplication of blastomeres or of the cells having each the potentialities of an ovum ceases when the quantity of elaborated growth-materials in the original ovum is reduced by subdivision below a certain minimum in each separated segment.

In this way the idea is perhaps made a little clearer of something which may be called formative force, guiding and directing the developmental changes in an embryo, which is not merely a direction of the cell-proliferation, but may exist also apart from any concurrent cell-proliferation, as well as coexist with it, as indeed it commonly does in nature.

It is, however, certain that, even although an increase of the number of blastomeres of an ovum ceases at some period of its development, which apparently corresponds to that at which its own stores of elaborated growth-materials are exhausted, or nearly so, yet is the faculty of cell-proliferation not lost, but only suspended; for the normal free larva grows, develops and proliferates cells in abundance, if, in the environment, it manufactures or finds suitable growth-materials; and unless it does so

it soon dies; while, if it finds or makes them, the cell-proliferation is constant in all organisms, and with it also their differentiation and development, involving life-periods and death of parts and individuals, and always a provision in advance for the production of new organisms and for their dispersal.

Many examples can be pointed to of the co-operation of the so-called formative force with the cell-proliferations in the reproductive regeneration from fragments of the lower animals, *e.g.* longitudinal sections of a hydra, or transverse ones of planarians; and in some the latter seems or is said even to predominate; but in nature as a whole the function of the former seems mainly to be to direct the order and arrangement of the proliferated cells, and in some way, perhaps, to influence their individual developments.

Too little is known, at least to me, of the details of the developmental changes of form and structure without cell-proliferation, such as are sometimes spoken of, in the production of a free larva from a blastula or from a segment of one, to justify much speculation, or to enable it to be profitable; but I am tempted here to suggest that in these cases of intrinsic developmental changes of existing cells, if they really occur, the metaplasiæ or differentiations are probably always attended with some proliferations of the structural units of the cells, or of some of them, even if it be at the expense of others, in the same organism, or fragment of one.

The view here suggested of a formative force as a factor in these regenerative acts, and as distinct more or less from cell-proliferation, does not invalidate the fundamental doctrine that the cell is to be regarded as an elementary organism, nor that its most constant and essential character is its faculty of division or of prolifera-

tion, which, as long as the life of the cell endures, is never quite lost, although it may be suspended for a time; for it can be restored when the conditions which had suspended it are replaced by conditions which favour it; subject to the qualification that the cell shall not be quite mature, or so highly specialised as to have thereby ceased to live a vegetative life as a whole, although its structural units may still proliferate.

§ 51*e*. Reproductive regeneration, then, or regeneration of organisms as in (*c*), after injuries, casual or experimental, is a very instructive thing to study in regard to *Repair* as a whole; and taken together with (*a*), cell and tissue regeneration, and (*b*), organ regeneration, it helps much to show us how complex and intricate a mechanism is the automatic reparator, thought of as a whole, especially in the higher organisms; how varied may be its manifestations in different organisms, or parts thereof, or in different life-phases; and so it helps to make at least partially intelligible some of the diversities, partly of an intrinsic origin, which it so often exhibits in malformations.

For example, the malformations, abortions and dwarfs require that we take into account the injuries which cause or condition them, not only in cell and tissue regeneration, but also in organ and organism regeneration; and we must remember that any one of these malformations may be met with in different parts of different organisms, even if adults, and may then be much admixed; and any or all of them may also be perturbed in a host of ways and degrees, given only perturbing causes, that is, irritants, which are rarely long absent.

There is, however, here reserved, provisionally at least, the question whether all the responses to all perturbations of the reparative faculties or mechanisms are to be con-

sidered as true *Inflammations*, or only some of them, and if so, which. The reply to such a provisional reservation is at present that, as perturbations of the reparative faculties are here thought of as equal to "injurious irritations," they alone signify *Inflammations*, and that the abnormalities of repair, which do not necessarily include "injurious irritation," alone are responsible for the production of malformations of all kinds and degrees. I have already said that all *Repair*, and therefore all regeneration as such, is to be regarded as essentially intrinsic and normal, although often initiated and conditioned by a casual injury; and also that, although *Inflammation* is a perturbation of *Repair*, and so of regeneration, it is expedient and justifiable to regard such reparative regenerative responses to a simple injury, whether in the groups (*a*), (*b*), or (*c*), as only normal consequences of the action of "the universal physiological law of nature," without any further interference of an "injurious irritation," as not *Inflammation*, and indeed not as responses to true perturbations of *Repair*; even when, as often happens, the reparative and regenerative response does not result in an exact or complete regeneration or a true *Repair* of the loss or defect, but is only an imperfect compromise, that is, a sort of malformation. In this way, a regenerative act of the (*a*), (*b*), or (*c*) type may lead to or result in a malformation of some sort, or an abortion, or a dwarf, according to the site or extent or character of the primary injury, and according to the intrinsic faculties of the injured organism, or of its part, without the occurrence, as etiological factors in the process, of any extrinsic interfering forces or irritants, and so without a true perturbation of the reparative powers, which are acting then quite normally for the conditions present; and yet it, the regenerative act, then often

determines results, or yields products, which are in many cases not beneficent, and often are harmful; and they are the true responses to an abnormality of repair, as distinguished from a perturbation of it.

In these cases it is assumed that the primary injury is effected at one act, is not repeated, does not persist, usually is massive, and always produces some loss or defect; so that the resulting malformation, or abortion, or dwarf, is imperfect as a *Repair*, in consequence of some incompetence of the automatic reparator, acting under the conditions imposed by such injury, that is, under the conditions of an abnormality of the repair faculty. Such incompetence is perhaps best shown in such an example as the development of a dwarf larva from a segment of the blastula of a sea-urchin; but it is also seen in the want of perfection of a scar-tissue in man, after a suppuration, or in a healing by granulation; in which, however, the imperfection is less, and the whole relations are more complex—are, indeed, never quite free from some previous admixture with true perturbations of *Repair*, or the responses to irritation, and therefore from some true *Inflammation*.

We may therefore, by this theory, rightly consider all malformations, abortions, dwarfs and their allies, not essentially as responses to perturbations of *Repair*, seeing that all can be, or rather are, consequences of inefficient efforts at *Repair* and regeneration, under the abnormal conditions of their production; which conditions are such that the automatic reparator is not then competent to restore the norm, although by the law of its being it must make an attempt to do so, and in so doing makes but a poor compromise, or fails utterly, being dominated by the condition, abnormality of repair, and not by any extrinsic irritant or perturbator. In concrete cases, however, it is

rarely, if ever, that we find such a complete absence of interfering forces and of "injurious irritation," and of the responses thereto, as the theory demands; for in a pure regeneration or *Repair* almost always some interfering forces come in, some "injurious irritations" take place, derived always extrinsically as regards the part, though not by any means always extrinsically as regards the organism; and these then involve responses, which are the expressions of a true perturbation of *Repair*, and are therefore indications of an *Inflammation* proper, and show then relations of fitness to the irritant, the perturbing cause, and this most obviously when the irritant is a parasite; less so when it is a physical or a mechanical agent merely; and least of all when it is an intrinsic hindrance and a necessary consequence of the complex structure of the organism, such as I have called above a hindrance to *Repair*, in man. But in all cases such responses to "injurious irritation" are antagonistic to *Repair* and to true regeneration; they do harm to the part and to the organism; they may entirely prevent *Repair*, or may destroy the part or the organism; and although due fundamentally to the same reparative faculties which, when not so perturbed, result in a *Repair* or a fair compromise thereof, yet, when misdirected by a persisting or repeating irritant in action, are themselves no longer reparative, but often destructive, always damaging and regressive in various ways. Such responses, then, are true *Inflammations*, and are further distinguished from the malformations by being terminable, in the ratio of the relative diminution of the irritation, when a *recovery* commences and may go on.

Yet, although the truly reparative responses after an injury begin at once, the products thereof normally endure long after the injuries have been repaired; and they often

functionate, perhaps imperfectly, yet usefully for the organism, and thus they differ from the inflammatory responses. Sometimes, when abnormalities of the reparative faculties are present in but a slight degree, the responsive products may approach to various malformations such as we call deformities, as may be seen in scars, and after some fractures, and also in some non-malignant new growths.

But, although in concrete cases pure *Repair* is rare, or perhaps never seen, at least in the highest organisms, the theoretical view of its essential and necessary distinction from *Inflammation* and from malformation is justified by the facts, which show such an approach to it in a perfect form as to make it certain, using the argument from the imagined converging lines, that a point of intersection must be, and pure *Repair* is.

§ 51*f*. In this theory, then, malformations, abortions, dwarfs and deformities are clearly separable from true or inflammatory perturbations of the automatic reparator, and are to be thought of as due to other abnormalities or imperfections thereof, under the given conditions; but in fact, in concrete cases, they also are almost always admixed with some true inflammatory perturbations of it, and with the responses thereto, by which as a whole the phenomena are obscured, and the theory is thus, at times at least, apparently controverted; but yet is it not so upset.

Some malformations and some dwarfs may present very little of such admixture, and some, especially of the former, more, but abortions usually more still, while many dwarfs may be fairly perfect, and may even seem normal, or nearly so; and the same may be said of some deformities and scars.

In the hope of making clearer this conception of the various abnormal results of those inefficient reparative

regenerative efforts, which should not be called perturbations of the reparative faculty, and so not *Inflammations*, but malformations, I will refer here to an ill-defined, but large and very interesting group of them, to which Loeb has given the name of heteromorphoses; and without adopting all his views, I will give some examples, such as may mark off these abnormal products of regenerative action from typical inflammatory responses to irritation with sufficient clearness; even if again a margin may remain less typical in their characters as presented, and more difficult to group in their natural and true relations.

Thus, if a salamander renews a cut-off tail, a newt a separated leg, a worm a head or a tail, in its due site and with the form, structure and faculties of the part removed, the process is one of a normal regeneration of lost parts and of a *Repair* of injury. But, if a worm abnormally regenerates a tail at the end where the head has been removed, as it sometimes does, without the causes thereof being well known, although the newly produced part appears to be perfect in structure as a tail, it is for the purposes of the organism worse than useless, and it does not complete a viable organism, which must then at no distant time cease to live. Such an abnormal regeneration is as damaging to the organism, as the organ so produced is inefficient, and does not replace the loss; it is an example of a heteromorphosis, of a kind which has very important consequences. This group of malformations is very large, is variously manifested, and it is not so well defined as is wanted; it includes also such cases as the abnormal regeneration of an antenna, where a stalked eye has been removed from a crab or a prawn, and, so far as has been seen, without much of loss to the organism by the change; and the new organ produced is like one proper to the same organism at another part.

But some cases may here be included also, such as those in which a new claw or leg is produced which is unlike any other proper to that specific organism, as is seen sometimes in the shrimp *Atyoida potimirum* (Morgan, *l.c.*, p. 24), and also others in which the new organ regenerated is the mirror-figure of the lost one, *i.e.* has its axes reversed. Most of these heteromorphoses seem to be useless or even injurious to the affected organism.

But the term, as it is used, may include also cases in which at least some degree of apparent usefulness to the organism seems to be sometimes involved, even although the product is a sort of malformation, or a monster, thus including a kind of abnormal regenerative reproduction. Such are the many-headed hydræ produced by making several short longitudinal cuts through the hydranth; and the same is seen in the double-headed planariæ, or earthworms, or in the new and wrongly placed heads, more or less efficient, on a *Cerianthus membranaceus*, or a *Ciona intestinalis*, made by cuts almost anywhere into the body of the organism.

Although these are all malformations and abnormalities of repair, and, it cannot be doubted, damaging, yet in some of them the result is, in some degree, such as may increase the chances of life for the organism, and probably, in the case of a hydra, very greatly so. The response is then an admixed one, doing good and harm.

Thus this term, heteromorphosis, as it is used, includes some monsters, malformations, or other abnormal regenerative responses; some of which are fatal in their tendencies, others are or may be even useful to the organism, so as even to increase its viability, perhaps beyond the norm; and yet they are results of responses to injuries. Yet all are related to, or are forms of, abnormal reparative or regenerative responses to injuries;

in which, so far as observation goes, the agent of injury has quite ceased to be a persisting factor ; and the chief if not the sole factors remaining involved in the responses are the intrinsic reparative ones, abnormally varying, doubtless necessarily, with the remaining regenerative attributes of the part of the organism which had been injured, and with the extent, position and characters of the primary injury. Such intrinsic, reparative, regenerative attributes are usually assumed by the special students of ordinary regeneration as being normal and as operating without the intervention of any extrinsic interfering forces or "injurious irritations" of which notice need necessarily be taken ; or these, if present, are taken to be mainly hindrances of intrinsic origin only, such as are promptly overcome and have relatively little importance in determining any of the abnormal results of the series of changes, if they occur, and as having been, in fact, provided for in advance in the evolution of the automatic reparator.

In the study of the abnormal and irregular results of reparative regenerative actions, therefore, no notice is usually taken of extrinsic intervening "injurious irritation," as it is assumed to be absent, or negligible ; and this is a justifiable position, even although in fact it can scarcely ever be really absent, or entirely without effect. The phenomena presented are in so preponderating a degree held to be related as responses to some initial injury, and to the intrinsic regenerative faculties as abnormally conditioned, that "injurious irritation," as an intervening factor, is not needed ; while yet, to the organism affected, the responses may be beneficent, or the reverse ; and they are all determined by some abnormalities of the reparative faculties, the causes of which are as yet not adequately known. Such results of, or responses to,

an abnormality of the reparative process are not therefore perturbations of the process of *Repair*, such as occur in *Inflammation*, in the sense in which I use the term, that is, as responses to "injurious irritation." They are known as malformations; and, both on grounds of reason and expediency, the two ideas should be separated, however nearly they are related.

The closeness of such relations, at least in some of the products of the process by which malformations are brought about, and of some of the repairs by compromise, and of some products of the responses to "injurious irritation," is such as may excuse this lengthy examination, which may, however, I hope, have shown some of their connections and distinctions, even although in this way the statement of the comparisons, and the contrasts, may have involved some recapitulations both of facts and arguments.

§ 52. I will now attempt to show some of these comparisons and contrasts; but I must first interpolate a frank avowal that, in what has been written above in respect of the malformations, thought of as responses to abnormalities of *Repair* and as distinct from a pure *Repair*, or from an *Inflammation*, I have by no means made any approach to a complete statement of the various kinds and degrees of the teratological disorders which experience has made us acquainted with, or of their real association with *Inflammations*.

A common opinion among pathologists and teratologists is that the abnormalities called malformations are mainly, if not solely, produced in embryonic stages of the life of an organism, or in embryonic cells or tissues, and on this ground they are sometimes classified. It is also very widely held that they are especially heritable, that they are seldom found to begin in adult tissues or organs,

or at least not in the mature parts of these, and when so met with are not responses to any local irritant actions, that is, are not *Inflammations*, but are, as it is said, congenital, or in some way due to a series of changes induced in some unknown way in uterine or in ovarian life ; yet do these two ideas not conflict with each other necessarily. This doctrine is supported by many observed facts ; but these do not justify the adoption of the criterion of the embryonic or congenital origin of all malformations as a basis of their classification and a ground for their distinct separation from *Inflammations.*

For, although it has been demonstrated, as some of the examples I have given help to show, that malformations can be experimentally brought about in ova and in embryos, and in many of the lower animals and plants, which are biologically related to embryonic stages of higher forms ; and it has not yet, so far as I know, been equally well shown that the same can be done in the higher forms, in their more developed and mature tissues and organs, or perhaps even in the more embryonic parts which they usually contain ; yet it has not been conclusively shown that in any of these groups the tacit assumption of the students of regeneration of the complete and constant absence of irritant actions has been proven for all stages of development of an organism or of a malformation of one.

This is therefore still an open question, or at most it is only a probable assumption.

It has also been demonstrated that some malformations are inherited, and may reappear even for a long succession of generations, under apparently normal conditions of the environment—and this both in animals and plants ; but it has not been conclusively shown that, in these cases, the concurrent influence of irritant actions in the prenatal

stages is really as completely absent as it is usually held it is, on the ground apparently that it has not been traced. Nor have all other abnormalities of the repair faculties been adequately excluded. This conception of heredity is, then, also an open question, or a more or less probable assumption, if it be applied generally.

It has already, in dealing with the responses to irritant actions in plants or animals, been sufficiently shown that the younger and the more embryonic stages of the tissues or organs show the characteristic inflammatory manifestations more vigorously than do the more adult forms, and even that some few of these latter may fail utterly so to respond.

In this respect, then, the responses to "injurious irritation" act under somewhat like conditions, or at least in some respects may resemble the processes which yield malformations; and although less is known of any similar responses to irritant actions in ova, or in any prenatal phases of life, yet it is not at all said, or meant to be implied, that in these phases such irritant actions and responses thereto do not occur. Rather, I do not hesitate to say, partly as a result of my own observations, that they do occur and can be traced in some cases, though by no means in all those in which they can yet be confidently inferred; as in the cases of some germinating seeds, and of some living, even if not fertilised, ova, *e.g.* those of the pike, which in water respond to irritations, in modes which recall the changes in separate fragments of cytoplasm without nuclear-plasm, and may show resemblances to imperfect cell-proliferations.

It seems clearly to follow, that in the same or similar life-phases the abnormalities of reparative faculties also act and are responded to in the production of some malformations; indeed, on this point examples have been given.

To make these rather broadly put statements clearer, I will attempt to give a few examples showing malformations and *Inflammations*, separate and admixed, in embryonic and in adult phases of life, in plants and in animals, especially in the former, in which the points considered are, I think, often more clearly displayed.

Fasciation is a common malformation in plants. It consists usually, I would say essentially, in an irregular multiplication of parts of the organism affected, usually of axes, but then often as partially fused or as imperfectly separated. It is displayed also in leaves, flowers, or their members, often in buds, and then often with a disorderly and even a damaging arrangement, with multiplication of organs or members.

It is well exhibited in, and is congenital and hereditary in, the *Celosia cristata*, and to a less extent in *C. plumosa*, the seeds of each of which, regularly in *C. cristata*, and less so in *C. plumosa*, produce annual plants with fasciation of the stem and separate multiplication of buds, of a kind and degree which is a damage to the organism, however interesting it may be to the horticulturist. It is known that in *C. cristata* this malformation is hereditary, and has been so for three centuries; but as yet no injury has been distinctly traced in the seeds or in the seedlings, although these latter exhibit fasciation as soon as they are an inch high; and no evidence has as yet been afforded of any "injurious irritation" co-operating in the responses or series of changes, or of any other causal factor in the seeds of extrinsic origin.

Fasciation has, however, been observed by myself in an elm, *Ulmus montana*, not as a constant but a frequent effect of an "injurious irritation" caused by phytopti living and propagating in the buds. It occurs in other elms, from other to me as yet unknown causes, but so

rarely as to leave in my mind no doubt of the fact as above stated in regard to *U. montana.* I have been able, in this elm, to trace some of its stages and phases from the deposition of a single phytoptus egg upon the apex of the growing point of a very young bud, in succession through a series of years, and then as admixed with many and quite obvious damaging responses to "injurious irritation," including regressive and proliferative progressive phenomena; and the production of such fasciations is often or usually combined with that of other malformation productions, such as witch-knot formations.

In the course of these observations, evidence enough was accumulated to show that the fasciation had been begun by the irritant actions of the parasitic phytopti, and that the responding tissues were very young or meristematic groups of cells approximately embryonic in their characters. But the steps of the process by which such irritant actions sometimes did set up fasciation, and sometimes did not, I have not yet learned. Always inflammatory responses or their equivalents were present; always with these there were also present some regressive changes in the tissues, related, I think, somehow to the different types of malformation which followed, in modes which were not well made out; yet, in some way these malformations were always connected intimately with an *Inflammation* process during their production, even if only indirectly.

But in association with the "injurious irritation" set up by the phytopti, fasciation and witch-knot productions were not the sole or even the most common manifestations of the response. This was rather as a rule a swollen bud, with a thickened and deformed axis, with too many and disorderly placed appendages, including both buds and modified leaves. These are well seen and common on

the silver birch, the hazel and the black-currant bush; associated on the silver birch, often, not always, with witch-knots and some other malformations, but very rarely so on the hazel, or on the black-currant.

Such association of malformed buds and witch-knots, when it is found, is a casualty, certainly not a constant, in the silver birch; for I have observed one of these trees abounding in the phytoptous malformations of the buds and shoots for several years in succession, without a single witch-knot; and other neighbouring trees of the same species with witch-knots, but with no discoverable bud-malformations due to phytopti. Although the witch-knots have been imputed in these cases to the influence of the phytopti, in some modes not traced, it is now more generally accepted by phyto-pathologists that they are more constantly related, as are many other witch-knots, to the influence of—that is, the "injurious irritation" caused by—some parasitic fungi, as, *e.g.*, in the wild cherry and the silver fir.

In all of these cases, whether with or without phytoptous infection, there is some "injurious irritation" exerted by the phytopti, or by the fungi; and so there is present a real equivalent of *Inflammation* in these plants, and yet it is somehow etiologically related to a malformation production, that is, to an abnormality of *Repair*. In all of these instances of malformed phytoptous buds there is some progressive cell and tissue proliferation, with a perturbation of their modes of response; and also there are regressive phenomena, with some local necroses, which in all seem to be connected intimately with the production of the malformations, of whatever kind.

Inflammation or its equivalent thus in these malformations seems to be a necessary part of the series of steps, or of the process by which they are brought about; and

the question is thus raised as to whether it is legitimate to group them in quite a different category from that in which *Inflammations* are placed. I am, if with hesitation, now obliged to place them for the present in a greater group of responses to "injurious irritation," and so have to grant that some malformations at least can be traced back in part to "injurious irritation," persisting or repeating; but in any case they have a complex etiology, and the responses are correspondingly admixed.

It is, as has been said, a common though not a constant or a diagnostic character of *Inflammation* that it is terminable; but in the inflammatory responses to irritation in plants the products mostly necrose, and are then either enclosed or separated, and the delayed *Repair* or *Recovery*, if it does take place, is a scar or a compromise formed by and in almost normal tissues near. In this respect most of the malformations now being considered behave as do the later products of an inflammation process in a stage of recovery. The above-mentioned swollen and malformed phytoptous buds and shoots, although they sometimes in the silver birch may live, grow and develop on their own lines in the direction of the axis for four successive years, yet in the end all die, fall, or are cut off, as are other dead axes.

Yet, these responses show in their characters, with sufficient clearness, the characteristic features of true malformations not less than they do of *Inflammations*; and they are to my mind at present inseparable from either group, or rather they are cases in which the process is too much mixed for all the examples to be correctly classified.

The witch-knots, however they originate, live longer, often for more than twenty years on a silver birch; but among them also there are some which tend to die, decay

and be cut off, as one may see in a witch-knot seen now and then upon *Ulmus camprestris*, often of large size, and when young showing multitudinous crowded young buds and shoots, and, when old, appearing as irregularly formed and decaying solid masses of dead tissue, representing the core of the old witch-knot.

The fasciations also in this respect vary very much ; but their varieties are, I think, not very well known, or their life-periods, although some endure, as in the cockscomb, for all the life of the plant, and others, as in *U. montana*, die much sooner.

§ 52*a*. On the whole, then, the lines of demarcation between the inflammatory responses to "injurious irritation" and the production of malformations imputed to other abnormalities of the repair faculties cannot be well and clearly traced in all cases, even if it be true that theoretically a separation is both reasonable and expedient ; and so the two different pathological groups of phenomena are left with some very close, indeed inseparable and essential relations. This conclusion applies to plants and animals, I think, equally, so that further examples from among animals are not required.

This position sustains the doctrine that the two processes of *Inflammation* and of malformation production are or may well be placed in one common greater pathological group.

I do not think any phase of the life of a cell, or of an organism, really limits the responses to "injurious irritation," and I hold that, even in congenital morbid products, the earliest prenatal responses or changes may possibly have been so determined—as much so, indeed, as malformations otherwise caused—and thus, that we may have congenital inflammatory products, and even possibly hereditary effects thereof, almost as certainly, if not so

frequently, as we have hereditary malformations, or varieties.

I do not think that any organism, or any elementary part of one, is exclusively the seat of malformation production, and I hold that this pathological change, not less than *Inflammation*, can begin in any tissue in which are present the evolved reparative faculties of nutrition and growth, however adult it may be, if only it be not very highly specialised or too mature; as in such a case it always contains some cells or tissues capable of proliferation, because still living; though in some cases only the structural units of cells may be able to proliferate, *e.g.* as in some ganglion cells.

Notwithstanding the occurrence of these large groups of phenomena, in which malformations and *Inflammations* cannot be adequately or clearly separated, I am still disposed to adhere to the general conception above given, of a reasonable and a convenient separation of the teratological series of phenomena from the inflammatory ones, at least in a general pathological theory.

§ 52*b*. The various malformations, theoretically considered, do not, however, demand, as necessary factors in the process by which they are brought about, any "injurious irritation." The factors in such a process are, at least in the theory, only the evolved reparative or regenerative faculties, and some injury which, although its cause has then ceased to operate, has so conditioned the said reparative faculties as to render the responses inefficient, and incapable of effecting a true *Repair* or a regeneration proper; while yet obliging the cells or tissues to respond somehow, often in a disorderly or inefficient way, which, by the theory, is not directed by a then acting irritant, or in any way fitly related to it.

Of this sort of inefficient response to injury, examples

have been given above, in dealing with the production of dwarfs, abortions, monsters and other malformations, by experimental inquiry and observation. But all this is necessarily connected with the proviso that these malformation cases are really unmixed, are theoretically and in fact not *Inflammations* ; but such cases are perhaps few in nature. Many malformations, especially those often called deformities, and many scars, often show in their structures and functions some relations of fitness to the injured organism or its part out of which they spring ; and they may endure as long as does the equivalent normal part ; and such unfitness of their relations to the responding organism as they also sometimes show, is not known to be fitly related to any extrinsic irritant or agent of which we have any knowledge, except where there is or has been an "injurious irritation" and responses thereto as an admixture, as in scars, and in the experimentally produced deformities, abortions, dwarfs, or monsters, in which the products are as complex as was the etiology and the process.

The more fitly related responses, as in scars, closely resemble pure *Repair* responses proper, of which they are compromises, are rarely the seats of regressive phenomena, are in quantity largely proportionate to the injury, and in quality to the tissues actually responding. They begin after the agent of injury has ceased to operate, the injury only persisting, and the end of the process is not reached, if the organism lives, until the above-mentioned relations of fitness to the organism or its part have appeared, much as in a simple *Repair* ; and then the effective operative factor is the evolved intrinsic reparative regenerative factor, though then often it is so conditioned as not to be quite efficient ; and hence the result is but a compromise.

The theoretically assumed absence of any extrinsic

irritant agent, is an adequate explanation of the absence of any relations of fitness to such irritant, and of any regressive phenomena so produced, and the inefficiency in the responses which make the product rather a compromise than a true *Repair* depends upon the direct or passive effects of the primary injury to the responding thing. It is also true that these responses, so closely related to *Repair* and so strongly progressive in their characters, have many near allies in some of the more pronounced malformations produced experimentally; and thus no sharp line of demarcation between them is known to me, nor any between them and the most inefficient and damaging malformations, such as abortions, in which, theoretically at least, no inflammatory responses are necessarily admixed.

§ 53. It is, then, certainly difficult, although it is possible, to distinguish malformations from *Inflammations*, if we take into account and compare their various characters with care.

What, then, are these characters? and what are those by which both are distinguished from a simple *Repair*?

As both the responses to or after abnormalities of *Repair*, and the simple reparative ones, have been given at sufficient length above, I let them pass here, and take up now for comparison and contrast, even at the cost of some recapitulation, those which characterise the responses to "injurious irritation," that is, *Inflammation*, as it is the special question discussed in this essay.

In the inflammation process, not all the factors involved are quite the same as those engaged in a simple *Repair*, or in the production of a malformation; the processes, therefore, are not alike, and so the products differ in some very important particulars.

(*a*) In it a massive or other injury, a loss or defect, may be present or absent; so that it is not, as in a *Repair*, or in the production of a malformation, a constant factor. (*b*)

In it "injurious irritation" is a constant, while, at least in theory, it is not so in a malformation production, or in a *Repair*. (*c*) In it some reparative regenerative effort in response to the irritation is a constant, for the response is a vital action; but such effort is always during the process a failure, and is inefficient in respect of *Repair*, or of regeneration; but such regenerative yet inefficient or abnormal effort is also a constant in the production of malformations, although the product of the response is not then fitly related to the causal injury. (*d*) In it, with this failure to repair efficiently, there is constantly present some damage or impaired function, the fifth sign, shown always in some regressive or necrotic changes of the part responding, which is not seen in a pure *Repair*, though common enough in a malformation. (*e*) In it the product of the response is always inefficient and damaging to the organism; but it presents specific relations of fitness to the irritant agent, and this is not so in *Repair*, nor in a malformation proper. (*f*) In it the evolved reparative faculties are not less constantly present and operative than in a simple *Repair*, and in the production of malformations. (*g*) In it the massive injury, though not a constant concomitant, is a frequent one, and then it may serve as a contributory factor to the action of the extrinsic irritant; and it may be simply repaired, or may later on condition some additional form of "injurious irritation." (*h*) In it the constant concomitant, "injurious irritation," which is, theoretically at least, absent in malformation production, initiates and measures the inflammatory process itself. During this irritant action the response to it persists, and so it is measured in the various phases of the process displayed; and as it diminishes or ceases, the responses correspondingly cease or diminish, and then recovery begins and goes on, so as to involve an ultimate

Repair of any initial massive injury, if any had been, and also of the above-mentioned damages or regressive changes, which had always shown some relations of fitness to the irritant agent, but none to the responding organism or its part. (*i*) In it thus the whole process of inflammatory perturbation of repair begins, continues and ends under the direction, or rather misdirection, of the irritant, either in the presence or in the absence of any perceptible massive injury, and, if such be present, quite irrespectively of or antagonistic to its *Repair.* (*j*) In it we have a series of changes which are terminable in recovery, but only if and when the injurious irritation either diminishes or ceases; so that *Recovery* is not a constant character, and is not met with if the irritation persists or repeats. (*k*) In it the product of the response is in part at least regressive, not persistent, that is, it does not endure as does the organism or its part, and it contrasts in this respect with simple repair products and with many forms of malformations or deformities, or compromises of *Repair*, such as scars. (*l*) In it the products of the responses are, as said, not persistent, because they are regressive, and not beneficent to the responding organism; but they always persist long enough to benefit the irritant, to which during all their phases they are fitly related, as is especially well seen in parasitically caused *Inflammations*, and especially well in plants.

Thus a comparison is drawn, by which adequate contrasts and distinctions are perceptible, between a simple *Repair*, perturbations thereof, that is, *Inflammations*, and malformation production; even although at the same time the close, intimate and essential connections of all three appear with so much vividness as to make an absolute or rigid separation not always possible.

The malformations dealt with above as abnormal re-

generative efforts include heteromorphoses, and both are placed on one side of an ideal line, on the other side of which stand the inflammatory perturbations ; so that it is to me quite inadmissible to place, as O. Hertwig has done, plant galls among the heteromorphoses.

§ 53*a*. No vital responses to "injurious irritation" known to me show more convincingly than plant galls do that they are inflammatory perturbations of *Repair*; seeing that they begin, progress, are fitly related to and end under the direction of the irritant, and show clearly the required distinctions from the heteromorphoses and other malformations. O. Hertwig truly found the study of plant galls very useful in connection with his question, that is, the significance of epigenesis *versus* preformation ; but his pursuit of this question by no means justified his placing plant galls among the malformations and the heteromorphoses, and so to separate them quite from *Inflammations*, to which they are so much more closely related.

Neither is there any true or close analogy between such instances of heteromorphosis as Loeb refers to, in which sometimes structurally and even apparently functionally normal organs are produced in abnormal positions in plants or in animals, and gall-growths, which, wherever they are placed, are always more or less heterologous in structure, functionally are adverse to the organism which responds, and are specifically fitly related to the irritant cause of the series of changes, while they present few if any indications of any close alliance with true malformations or with heteromorphoses of any order.

The growth of apparently normal roots, under good cultivation conditions, from some small masses of gall tissue which are no longer related either to the gall-producer or the host plant, except in structure and by

descent, such as we see in some Nematus galls on *Salix purpurea*, is not easily classified in any known group, that is, either as *Inflammation* or as malformation.

Such root-growth from a gall is not a simple *Repair* of it, or a perturbation thereof, nor is it directly due to any "injurious irritation," of the part or of its tissue, even if indirectly it has had some association with a previous irritation, of which perhaps later effects may result in some way by a persistence of motion.

It is not a simple *Recovery* nor a true malformation, although it approaches more nearly to a heteromorphosis than to any other of these abnormal products, seeing that it results in the production of a normal organ in an abnormal position.

The factors in the process are the gall tissue, a specifically modified and perturbed one, with the evolved intrinsic regenerative faculties, as then present, and conditioned in such tissue, tending to revert to or towards a norm, not further perturbed by any new extrinsic irritant actions, but much influenced by good cultivation conditions of the environment, especially by moisture and heat. The product is essentially a normal organ, but it is not, and does not develop into, a normal organism.

The whole series of events resembles that in which a dwarf is produced, but one which is not viable. Therefore it seems reasonable to consider it as due to an attempt by an inefficient or imperfect responding mass to complete or produce a viable organism. It is in effect a heteromorphosis, or more like that than anything else. The newly produced organ is misplaced, it is not efficient, or is only so for a very short time.

This response is of great interest, not only in regard to the question of epigenesis, but also as an example of a reversion to, or towards, a norm of tissues which had been

perturbed and in which the irritant actions had ceased, though some of their consequences still persisted in the structures which had been produced. It may well be considered as an imperfect and failing attempt to *Recover*, a sort of compromise, and not a good one.

§ 54. If I have laboured here overmuch the consideration of the reparative faculties and mechanisms which are perturbed in *Inflammation*, as I understand it, it is partly because of their intrinsic, universal and fundamental importance, and partly because of the necessity of adequately separating those abnormalities of the reparative process which are more conveniently included in the term malformation from *Inflammation* and from *Repair*, connected closely as indeed they all are.

I have incidentally, in the course of the argument and its illustrations, so frequently referred to *Inflammation* as a perturbation of *Repair*, and have so often shown the chief characters by which it is marked off from *Repair*, normal and abnormal, that it is superfluous here to deal again with them, their causes or their consequences.

I will now therefore only say that in my view "injurious irritation" is the perturbing cause, and is the constant and necessary antecedent, or rather concomitant, of that series of changes in a living organism, or part, which has here received the name of *Inflammation* in all organisms; and it, the "injurious irritation," then stands related to the responses, as does injury to *Repair*, so that without "injurious irritation" there is no *Inflammation* in general pathology.

It differs, however, from injury in some essentials, which may properly be noted. Injury is a passive, often a locally fatal, effect of an action which has ceased; "injurious irritation" is a persisting condition of disturbance, or a perturbation of a living cell, or of a tissue, due

to the persisting and still acting agent of disturbance, the irritant, which deflects the normal path of, but does not arrest the intrinsic vital movements of nutrition or repair in the perturbed cell or cell-complex. It is slight or, as has been said, even cryptic; but its ultimate effects may be very obvious and progressive, when accumulated, because it persists or repeats, and it is always a concomitant of the inflammatory response, not an antecedent only.

It does not itself ever *directly* kill or produce loss or defect; although *indirectly* it determines the misdirected responses, or the regressive, even necrotic, changes which follow in some of the cells and tissues of the focus, and such responses frequently, perhaps always, produce some local death or defect, and are responsible for the constant damage.

The so perturbed, intrinsic reparative faculties are commonly excited by the irritation to an excessive, often progressive, local action, and the irritant, although always injurious, can and does stimulate or increase some of the local vital faculties, proliferative and other, while at the same time it misdirects them or deflects their path, so as to render the product damaging, disorderly, even heterologous, as regards the organism affected; though often, as in plant galls, it is clearly orderly in structure, and useful as regards the irritant.

In this way can be explained most of, perhaps all, the regressive changes in the product or the response, which result in a local death or defect, and also the progressive changes so constantly met with simultaneously—a conjunction of events which gave Virchow and other pathologists much concern to explain.

The irritant, and its direct effect, "injurious irritation," are, as I have said, never absent at the time and place where *Inflammation* is, even although an irritant may not easily be found. The irritant in action is that which,

through "injurious irritation," deflects or perturbs the evolved intrinsic normal functions, nutritive, formative, or other; and thus it measures as cause, all through the phases of the process, the effects, responses, or manifestations.

Thus thought of, the expression "perturbation of repair" is appropriate, as is also the idea of a persisting misdirection, so long as the process of *Inflammation* itself endures. For the irritant, as the cause of the "injurious irritation," misdirection or perturbation, obeys the law of all natural causation, and the effects show the same obedience, in the relations of fitness, always seen in the products to the irritant, however unfit they may be to the perturbed organism.

These relations of fitness to the irritant are best seen, I think, in plant galls, but they are also exhibited in many of the typical *Inflammations* in man, which are parasitic in their etiology, as most of them are.

Although true *Inflammations* are met with which are not parasitic in origin, yet are these the less typical forms, and in them the relations of fitness to the irritant here spoken of are much less obvious; yet they also, if considered in the light afforded by the study of the parasitic forms, are found also obedient to the law of equality of cause and effect, and show in the responses to traumatic irritations that the effects are fitly related to the causes, even when such relation is less obvious than in the parasitic cases. See especially the persisting or repeating traumatic irritations, and *Inflammations*.

The perturbations of the evolved intrinsic reparative mechanisms and faculties, that is, of the automatic reparator, so called forth by the irritant actions, through "injurious irritation," are manifested by the signs of *Inflammation* in man.

Of these signs, in all organisms, the most constant and universal are perturbed or disorderly, often excessive, always damaging exertions of the very faculties which, in the absence of "injurious irritation," but in the presence of a simple massive injury, effect a *Repair* proper.

These faculties are the evolved intrinsic nutritive and formative ones, of which the most universal manifestation is a proliferation of structural units of cells, and of cells themselves, with development into tissues, combined with a constant and necessary adequate supply of growth-materials.

Such manifestations vary in degree with the structures and faculties of the responding organism or of its part; and thus in some, that is, in the higher vascular and nervous ones, we often have heat and redness, pain and swelling, even so displayed as to dominate, and then to somewhat obscure in them, the proliferative signs also present, but not to hide the fifth sign, the damage, for this is constant.

These traditional manifestations are not, however, and cannot represent, the *Inflammation idea* as manifested in all organisms or in general pathology, as here the word is understood; for they apply only to some.

Thus, a constant manifestation is, I think, found for *Repair*, for *Inflammation* and for malformation production in all organisms, that is, in general pathology; which manifestation rests upon the evolved intrinsic reparative faculties, acting efficiently or not, perturbed or otherwise abnormally conditioned, and in this manifestation proliferations alone are never absent, although they are often diversely displayed.

However, *Inflammation* itself cannot be accepted as a faculty evolved in obedience to the law of survival of the fit; seeing that in it damage is a constant, as may be seen in the general acceptance of the fifth

sign, or of regressive structural changes as constants; and also in the fact, so much asserted, though also controverted, that it has not itself essentially or constantly any useful or salutary effect or purpose. *Inflammation*, be it remembered, is terminable often, though not constantly. It is so when the "injurious irritation" ceases or relatively diminishes, from whatever cause. This occurs often as a normally occurring part of the life-history of the irritant, when a parasite. Then *Recovery* begins and goes on; *Repair* dominates, and is or may be efficient.

When, as often happens, the irritant persists in action, or repeats, or spreads, then the responses persist, damage goes on, the process does not terminate, except perhaps in local or in general death, and *Recovery* cannot take place. Thus, the terminable character of *Inflammation* is not a constant, it is not a diagnostic, and in this way *Inflammation* is not separable from the process by which new growths are produced, nor from that which sets up malformations.

Inflammation is a local process, as is commonly and rightly taught; but the locality is not limited or defined, and at its periphery it is often very indefinite. It may spread through the whole of a large and complex organism, and be represented at different parts of the focus by different grades, signs and manifestations.

Always, somewhere, there is irritation and proliferation; but, in the focus somewhere, its signs may be found, even if indefinitely distributed, as heat or pyrexia, or as various chemical changes of fluids or solids, such as the production of toxins, antitoxins and allied substances, or phases of material, which, however, are not constant in all organisms, so far as is known; but when present as consequences of "injurious irritations," are signs of *Inflammation*.

§ 55. Difficult although it is, as so many failures have demonstrated, I cannot avoid making an attempt now to define my *Inflammation idea* in *General Pathology* in a short formula :—

In virtue of those evolved normal faculties, by which all living organisms repair waste and either normal or casual injuries, and without which they could not live, all living structural units of cells, cells, or cell-complexes react in response to "injurious irritation" by a proliferation with modifications directed by the irritant, often obviously for its purposes. Such responses are always fitly related to the irritant, as other effects are to their causes, but always they are misdirected as regards the organisms in which the process occurs, and are so unfitly related to them as to be always damaging. Although, as all organisms must be considered in a General Pathology, such modified, or misdirected, or perturbed proliferation is the only known constant and universal mode of response to injurious irritation, yet it is not the sole mode for some organisms. In some, as in man, it is less obvious than are the responses evinced after such "injurious irritations" by and in the blood-vessels and nerves ; but, even in these cases, such proliferations are never absent. These misdirected, perturbed responses are Inflammation, as it, or its equivalent, is met with in all organisms in General Pathology. It is distinguished from Repair, for it is a perturbation thereof. It is a casualty, a disease, and is not an evolved faculty, as is repair. It is distinguished also from malformation production, though by less well-defined characters, so that the boundaries of each may overlap, and be difficult or impossible to trace.

This attempted definition differs in no important particular from that given in the postscript to my reprint of the address "On some Diseases of Plants compared with those of Man" (1903), and it only varies the language a little, so as, I hope, to make the meaning more clear.

It, taken together with the long, and I fear often involved, descriptions given of the phenomena, their etiology and mutual relations, in such a wide field, is in harmony with the assumption I adopted at p. 16 of that address, that all reactions of living tissues to irritations are rightly considered as *Inflammations* ; but, with the qualification that all such irritations are to be held as concomitant, persisting and injurious, I adopt it now, as modified, after a reconsideration.

The difficulties presented in the examination already given in the results of abnormalities, of the intrinsic reparative faculties, as in the various malformations, heteromorphoses, deformities, *Repairs* and *Recoveries*, are explained ; seeing that, in the said examination, adequate distinctions are afforded in a degree not less positive than we find in many other comparable series of phenomena in matters biological.

This view justifies the observer often in concluding from the characters, structures, courses and fates of the responses themselves, even when neither an irritant nor any "injurious irritation" is demonstrable, that such causes were or had been operative ; and the reasoning, although resting mainly on analogical grounds, is legitimate ; and, if not amounting to a demonstration, is convincing in proportion to the closeness of the analogies ; and it is the best ground available for a diagnosis.

This inflammation idea has some recommendations in that it helps, if not satisfactorily to all minds, yet in some degree, I hope, to many, to remove some of the grounds of the "confusion," or, as it has been also called, the "anarchy," which is prevalent in the present doctrines regarding *Inflammation* ; and to connect the known phenomena into one intelligible conception, in a general pathology.

Thus, it makes all living organisms and their tissue

elements its seats, and it does not demand in it conditions and structures, such as blood-vessels and nerves, which are present only in some.

It recognises *Inflammation* explicitly as a disease process, in which damage is a constant, and it explains that damage. It separates this disease process adequately from the repair process, and it shows the kind and degree of the actual and necessary relations existing between this normal faculty, as a fundamental one in the disease process, and the said disease process itself.

It offers an intelligible conception of the complex etiology of this disease process, so related to and dependent upon an evolved normal reparative faculty, its prime mover, so to say, while yet determined as to its characteristic and damaging features by an extrinsic perturbing factor; and it explains also the relations of fitness to the irritant, displayed in a still living and progressively active tissue.

It, I think, clears up some of the difficulties presented to our minds by those who do not adequately separate reparative responses from inflammatory ones, but rather seem to mix them up together, in various modes.

It recognises the direct evolution of the reparative faculties by a survival of the fit; and it contests the conception of a similar direct evolution of the faculty to suffer *Inflammation*; while it grants an indirect evolution of the faculties, whether in the irritant or the host, or in both, which are operative in the disease responses.

It leaves out intentionally the greater part of the details or steps in the process, lest one should fail to see the wood for the trees; but it explicitly declares that one group of phenomena is a constant in all *Inflammations*, in all organisms, namely, a misdirected proliferation related fitly to its cause, the extrinsically derived irritant.

It recognises, mainly on grounds of seniority, or priority, that the type of the disease process is met with in man; but it does not grant that the characteristics most obvious in that type are the constant and characteristic ones in all organisms in general pathology; and it seeks the constant in that which is common amid the variable throughout the whole area.

It denies that inflammation is purposive, in the sense of being beneficent to the responding organism, or that it is preparatory to a repair, or in any sense a salutary process, or a healing power in nature, or that it cancels or removes the irritant; and it asserts that it is an effect of or a response to an "injurious irritation," which it measures, and to which its results are fitly related, as are other effects to their causes, so that, if purposive at all, it is so to the irritant.

It recognises that the process is manifested locally, while it grants freely that the limitations of the local changes are indefinite, and that it may involve the whole of the responding organism; and it also includes all the diverse phenomena which the injurious irritation has set up.

It asserts that irritant action, "injurious irritation," does itself induce true proliferations, and demonstrates this, at least in plant galls; and it denies that proliferative or progressive responses are only caused by the so-called stimuli, and are limited to repair processes.

It shows that the misdirected responses of proliferation are at least indirectly, often, if not always, in some degree regressive, and so may lead to degeneration and necrosis, and still are parts of the process of *Inflammation*; and it denies that they are, as has been said, no part of *Inflammation*; it shows in what way they are parts of it, and their relations of fitness to their causes.

It shows characteristic manifestations of the process by

which it can be recognised and diagnosed with approximate confidence, even in cases where the "injurious irritation," or the irritant, is itself not discoverable by observation.

It solves the difficulty, so often felt and expressed by pathologists, of the concurrent association in one focus of regressive and progressive phenomena, by explaining such association.

It disposes, I think adequately, of the difficulty which some recent publications have so much brought forward, of the relative significance of the intrinsic faculties of the organism, and of the extrinsic factors in the process, by showing their actual relations and interdependences, not only in it, as it usually is understood in typical *Inflammation*, but also in other allied and markedly proliferative responses, or groups of phenomena, such as the neoplasms, or tumours, especially in those which are malignant, and especially destructive, damaging and regressive.

It recognises and duly appreciates the immense significance of the etiological factors in the process, and it relates these to the effects, especially as displayed in the more instructive forms, that is to say, the parasitic ones.

§ 56. In this first part of the essay on *The Inflammation Idea in General Pathology* I have with intent given few and exceptional references to pathological authorities; but in the second part it is intended to correct this seeming neglect, and to present then and fairly appreciate at least so much of the work of past authorities in pathology as may show the development of the *Inflammation idea*: the organisms in which its manifestations have been studied, the characteristics of such manifestations as have been accepted by different authorities, the

etiological factors also as they have been accepted by different authorities, also the diverse and conflicting views which have been entertained as regards the essentials in it, and its consequences or "purposes"; which views have as yet not been harmonised into an accepted, connected, or intelligible whole; but have indeed rather left such a chaotic result, that Andral in 1832 and Thoma in 1886 frankly desired to abandon the word and the idea.

While very many of the ablest teachers have shrunk from formulating the idea of inflammation in a strictly limited definition, as, *e.g.*, Virchow, Paget, and Burdon-Sanderson, some others have framed strict definitions, often by limiting the *Inflammation idea* to certain animal organisms, or to certain tissues in them, or to certain restricted changes in those tissues or tissue elements, without adequate reference to other organisms, or to the relative significance of these restricted conceptions to allied or equivalent phenomena, often of similar etiology and having analogous characters, when seen in the same organisms which they study.

Of these definitions a selected characteristic series will also be given. In this way it will, I think, appear that, if a harmonious, connected and intelligible conception of *Inflammation* as a whole in all organisms in general pathology can be made clear, in respect of its etiology and of its characteristic manifestations, there will be a gain to pathological science; and this I venture, though timidly, to hope has been here attained, if not surely, yet with some degree of probability.

It is expedient for the reader always to remember that inflammation was formerly thought of, not as a part of *general pathology*, but as a group of phenomena, some of them subjective only, and chiefly exhibited in man.

In such a school of pathology I was educated in the forties of the last century; and doubtless I enjoyed then such advantages as are connected with strict limitations and definitions, as well as the disadvantages tending to want of breadth, which it also presented. At this date I had for teachers: Samuel Cooper, who advocated some of the doctrines which Hunter had worked against. Thus, he said: "In almost all the cases which fall under the care of surgeons, inflammation is more or less concerned either as a cause, a symptom, a complication, or even as a means or mode of cure": Liston, who worked hard and with some success to avoid or elude inflammation, and to secure healing by first intention: C. J. B. Williams, who was concerned chiefly with the steps of the process, and connected it chiefly, indeed solely, with vascular phenomena, and had much in his mind the leucocytes, and even W. Addison's observations: and Walshe, who in this field was concerned mainly with the problems of the mechanical and physical changes associated with inflammation, viewed from the standpoint of the pathological anatomist. In this way my mind was brought into relation with diversities of view which were for me very confusing, but at that time by no means uncommon. While it is granted that objects seen in a narrow field of view, such as inflammation presents to us in man, are more definite, it is not less certain that the visible objects in a wider area are so shown as to enable the observer better to judge of their relative proportions; and it is just this question of the proportionate significance of the phenomena observed in all organisms, which is here raised in the study of *Inflammation in General Pathology*. My present conviction is settled in favour of the *Inflammation idea* as it is above set forth; and it has been reached after as full and candid a study of past and recent authorities as is possible

to me, with a concurrent series of observations of facts carried on for many years. So that the second part of this essay, although it may show the paths along which my thoughts may have travelled in changing so much as they have done since my student life, will not be likely to reverse or fundamentally to change them, even if some new difficulties be shown to require explanation. For such a reversion would imply an abandonment of the broader field of view and a return to the narrower one, which would be in conflict with my individualism, and with the present tendencies of scientific *General Pathology*, as I understand the term.

For these among other reasons, I purpose publishing this first part in anticipation of the second, which I hope may follow.

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